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THE RELATIONS OF THE FEMALE REPRODUCTIVE ORGANS TO INTERNAL DISEASES.[1]

By Friedrich Müller M.D.,

PROFESSOR OF INTERNAL MEDICINE IN THE UNIVERSITY OF MUNICH, GERMANY.

Since through the coöperation of surgery with internal medicine a border zone of greatest productiveness has been developed, it is perhaps opportune that the border zone between gynecology and internal medicine should likewise be cultivated more than has heretofore been done. A not inconsiderable amount of pioneer work has already been contributed. In undertaking a sketch of this field, it will be of advantage: (I) To mention those internal diseases which have been observed in connection with the physiological processes of the female generative organs, namely, puberty, pregnancy, and the menopause; (II) to consider the significance of the pathological processes in the female reproductive organs which give rise to medical conditions; and (III) to discuss the relation of certain internal diseases to disorders of the female reproductive apparatus.

I. The period of puberty induces apparently much more marked disturbances in the female than in the male, and, moreover, in the somatic than in the psychic aspect. In regard to the somatic manifestations of disease, we are reminded of chlorosis, a prerogative of the female sex, which appears to be associated with insufficient hemoglobin formation. We do not find, however, sufficient evidence to prove an injury of the red blood disks already

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formed and of an increased destruction of the hemoglobin therein contained. In any event, the loss of blood during menstruation is insufficient to explain the enormous reduction in the hemoglobin which is found in chlorosis. In relation to the total volume of the blood of the body, the hemoglobin in chlorosis, approximately estimated, is often only 200 grams, while in a healthy girl it amounts to about 600 grams. During a single menstruation, as Hoppe-Seyler has shown, only about 8 grams of hemoglobin is lost.

It is worthy of note that, during puberty, thyroid enlargement has not infrequently been observed; this, as we shall see, may accompany all later phases of the sexual life of woman. This enlargement of the thyroid, which, moreover, is observed with equal frequency during puberty in the male sex, is usually accompained by palpitation, rapid pulse, irritability, and more easily induced bodily than mental fatigue, and deserves the serious attention of those responsible for bringing up children as well as of physicians. It is, however, doubtful whether all cases of abnormal irritability and rapidity of the heart action which occur during puberty are associated with disorder of the thyroid gland. Frequently, one obtains the impression, in many of these cases, that they are rather the consequence of excessive sexual excitement and particularly masturbation; and often when growth is over-rapid, there are indications of irritability and, indeed, insufficiency of cardiac action, with diminished blood pressure and tendency to syncope.

In contrast to the thyroid heart of puberty, there is sometimes found, associated with evident abnormal smallness of the thyroid, a certain mental sluggishness and the characteristic symptom-complex of juvenile adipositas nimia, which, off-hand, must not be regarded as identical with juvenile myxœdema.

The psychic changes which develop during puberty are very peculiar. I do not refer to the special psychoses which appear at this time, but to those slight psychic disturbances which are too insignificant to be included within the domain of disease, but which however, can give rise to many difficulties in the training of children. They, for the most part, manifest themselves by an overemphasis of the psychic life, by a tendency to mysticism, or in slight conditions of depression, such as premonitions of early death, or in delusions of restraint and persecution, in other words, in the ideas which also are present in hysteria. In young girls who have not yet menstruated, therefore, in whom there is imperfect sexual development and hypoplasia of the reproductive organs, one occasionally encounters remarkable psychic changes, taciturnity, marked hysterical manifestations, bodily and mental hypersensitiveness, disturbances of nutrition, and frequently an obstinate and almost insuperable constipation. The disease conditions of the later period of youth, that is, from eight to sixteen years, have heretofore been insufficiently studied. The direction of an adequate interest to the age

of late childhood and beginning manhood is a service that still remains for pediatrics to render.

Pregnancy is undoubtedly to be regarded as a physiological process; indeed, in many ways it is accompanied by beneficial consequences both physical and mental. The healthy woman after a favorably terminated puerperium becomes younger; she appears fresher, more energetic, and more mature than the unmarried girl of corresponding years. Favorable sequels, however, are not the only ones which follow pregnancy. Especially in delicate young women of the refined classes one sees now and then that the months following delivery are attended by a rapid increase in weight, indeed corpulency, and a sense of increased health; but this gain, after perhaps half a year, is quickly lost. The increasing desire for food gives place to loss of appetite, the weight falls off markedly and is less than before the beginning of pregnancy, and hand-in-hand with this decreasing energy asserts itself, which stands out the more prominently if upon the young mother there fall greater household duties, social obligations, and the care of the child. Along with this reduction in weight and with the impairment of health goes a certain irritability, an inclination to capriciousness and to bad humor, of which the young wife herself becomes conscious, and against which she struggles vainly. All the signs of true neurasthenia and, indeed, overmastering impulses may develop.

Such a condition may, indeed, become unbearable, and often the husband desires a new pregnancy, in order to bring this state to an end. As a matter of fact, in the course of a new gestation the health and body weight are again restored, but this form of therapeusis is inefficient so far as permanency is concerned. After the second and, still more, after succeeding pregnancies the above-mentioned symptoms and loss of strength again appear in an aggravated form, usually not immediately after delivery, but months later. This time it requires longer rest, greater care, and more correct dieting, best carried out in a sanitarium, to combat the neurasthenia. "Neurasthenia," however, is not the correct designation for this symptom-complex. It is much more a general disturbance of nutrition and loss of strength, a condition which I desire to term post-puerperal asthenia of young wives

So long as it does not reach an extreme degree, the vomiting of pregnancy is still to be considered a normal sign of pregnancy. To consider this vomiting as a ogether hysterical would be to reverse matters, if we did not have to admit that hysterical vomiting also can occur in pregnancy. The uncontrollable vomiting of pregnancy is only a gradual increase of this manifestation of pregnancy. It differs from the uncontrollable vomiting of hysteria in that it is much more severe and that by it the stomach is emptied of its entire contents. Whereas, in the so-called uncontrollable vomiting of hysteria the general nutrition suffers surprisingly little, in the

severe form of the vomiting of pregnancy this is totally different. In the latter we see emaciation of extreme degree and complete exhaustion amounting to the condition of being absolutely bedridden; and the ferric chloride reaction in the urine shows us the severity of the inanition; so that usually, to avert death from starvation, an abortion must be resorted to.

If we do not regard the sporadic vomiting of pregnancy as hysterical, we are warranted in considering also its increased state, the uncontrollable vomiting, as not hysterical. As a matter of fact, in these cases the suggestion treatment usually proves itself ineffectual. As in the case of the physiological vomiting of pregnancy, one sees that the pernicious vomiting usually disappears quickly after the end of the third and fourth months. It is possible that it is associated with those processes of pregnancy which, during the third and fourth months, cease to make their baneful influences felt.

In a considerable number of cases of persistent vomiting still other diseased conditions, of psychic or somatic nature, occur. These are, perhaps, so seldom recognizable, because they are not at once apparent in prostrated and bedridden patients. Among these may be mentioned loss of the knee-jerk, marked weakness, and, later, atrophy of the hand and leg muscles, after the type of polyneuritic atrophy; further, disturbances of memory, conditions of excitement and stupor, and, indeed, even optic neuritis. This entire symptom-complex, expounded by Möbius and others, and repeatedly observed by me, corresponds absolutely to many toxic polyneuritides. Even as these do not limit themselves to a degeneration of the peripheral nerves, but may involve also the optic nerve, the brain, and the mind, so, in like manner may the polyneuritis of pregnancy, which latter, in the majority of cases, is associated with uncontrollable vomiting. If the disease picture is so severe that life is endangered and the premature interruption of pregnancy becomes necessary, one observes that with the removal of the produce of conception, after a time all the symptoms of the disease disappear, the patient awakes as from a sleep, and has sometimes no remembrance of the previous period of suffering, indeed of the pregnancy itself.

The neuritis of pregnancy is not always distributed throughout the entire body. At times it involves only an isolated area, as, for example, the perineal nerve. In such patients there may be some doubt as to whether the nerve plexus has not suffered through pressure of the pregnant uterus. In the severer cases of general polyneuritis, however, there can be no doubt as to the toxic nature of the affection.

Rudolph von Hösslin, to whom we are indebted for a valuable study of the nervous diseases of pregnancy, states that multiple sclerosis frequently develops during the course of pregnancy, and that often it becomes progressively worse with such succeeding pregnancy.

It has been remarked that this diease occurs more frequently in women than in men.

In this connection Pierre Marie has recognized that multiple sclerosis not infrequently appears in the course of typhoid fever. I have seen cases in which, after typhoid fever, there occurred the outspoken picture of polyneuritis, with optic neuritis and psychic disturbances. In one of my cases immediately after typhoid fever a symptom-complex developed which at first resembled polyneuritis, but later developed into typical multiple sclerosis with predominant spastic symptoms. It is well known that in the beginning of multiple sclerosis optic neuritis with swelling of the papilla is not infrequently present and that only later does this pass into atrophy. In consideration of these facts, it may be concluded that a relationship may exist between pregnancy and the neuritis of pregnancy, on the one hand, and multiple sclerosis, on the other, which we must explain in the same way as we do the association of typhoid neuritis and multiple sclerosis.

Let us turn now to the cardiac disturbances of pregnancy. These occur, as does the vomiting, in the first months of pregnancy, therefore at a time when one can scarcely speak of pressure of the uterus on the diaphragm and on the heart, or of mechanical interference to the circulation. These disturbances of the heart manifest themselves usually by extrasystolic arrhythmia, which gives rise to the uncomfortable sensation of intermittent heart action, to precordial flutterings and dyspnœa. They are improved by the use of alcohol and caffeine. If these symptoms become especially severe when in the recumbent position, they force the pregnant woman to sleep with the upper part of her body elevated. During the second half of pregnancy these heart and pulse irregularities may entirely disappear. They also tend to be absent in the interval between pregnancies. Once present, however, they recur with each new pregnancy; indeed, they can at such times be more severe and persist longer, even to the close of gestation. With the advent of labor they cease and give place to the slow regular pulse of parturition.

Of what character are the changes which give rise to the arrhythmia of pregnancy, I am unable to state, the more so since blood pressure determinations in such cases are wanting. They can have nothing to do with kidney disease, as in my cases no changes were observed in the urine. It is also improbable that they depend on serious myocardial changes, since they ordinarily tend to disappear with the termination of the pregnancy. One can conceive of reflex phenomena, transmitted through the nervous system. W. Müller has shown that the weight of the heart in pregnancy undergoes a certain increase, which approximately is proportionate to the general increase in the total body weight. This increase in the heart weight may be interpreted as evidence that during pregnancy the heart has greater work to do, greater resistance to overcome. Since

the extrasystolic forms of arrhythmia are to be regarded, for the most part, as an indication of a certain disproportion between the cardiac strength and the resistance to be overcome, we are, therefore, warranted in regarding these irregularities as an expression of an insufficient or not yet perfected adaptation of the heart to the increasing demands of pregnancy. After observing that subsequent to repeated pregnancies there sometimes occurs a persistent cardiac disturbance, especially arrhythmia, which, in the course of time, leads to the fully developed picture of heart-muscle insufficiency, we must conclude, unless a cause other than repeated pregnancies has been discovered for them, that sometimes the cardiac disturbances of pregnancy are responsible for permanent injury to the heart muscle.

Very frequently, in the course of pregnancy, the thyroid exhibits a moderately soft swelling, which, in the majority of cases disappears after the termination of pregnancy. Not infrequently, however, a struma remains. The enlargement of the thyroid in pregnancy is usually not associated with symptoms of hyperthyroidism. Indeed, to the contrary, if hyperthyroidism or even outspoken Basedow's disease exists before the beginning of pregnancy, during pregnancy these manifestations tend to diminish or entirely disappear. Apparently, therefore, pregnancy exerts a salient influence on hyperthyroidism. Only after a certain time succeeding the termination of pregnancy does it reappear more marked than before. Now and then one also sees that symptoms of hyperthyroidism develop for the first time several years previous to the menopause; that is, after women have gone through a series of labors and, as a consequence of pregnancy, present a thyroid enlargement, but no symptoms of hyperthyroidism. I believe it is not impossible that the remarkable variations in weight, that is, the general nutritional conditions, as well as the nervous conditions, which we may observe in association with delivery and the puerperium, are in some way related to the function of the thyroid gland. As exceptions to the rule that pregnancy favorably influences hyperthyroidism and Basedow's disease, now and then there occurs, in individual cases, an aggravation of the symptoms of exophthalmic goitre during pregnancy.

There exists in the life of males no parallel to the menopause of women. In men the sexual functions diminish much slower, and they disappear in perfectly normal men first at a great age or not at all. In women, to the contrary, the climacterium makes a very deep impression on life. The woman hitherto in vigorous health, within a short space of time is changed to a matron, and it is evident that such a change cannot take place without consequences to the bodily and mental condition.

The realization that old age is advancing can lead to mental depression; associated with this the bodily vigor becomes dis-

tinctly diminished, and much that life formerly held of work as well as of enjoyment must suddenly be largely relinquished. During the period marking the close of sexual life a condition of psychic depression often develops, which corresponds to that already noted in puberty. Women who until this time resolutely and happily met the duties of life and concerned themselves only with the welfare of their surroundings, become anxious and full of cares, see everything in a gloomy light, and bestow upon their own health an anxious attention which was formerly unknown. Often insomnia also appears and a certain restlessness. Likewise, complaints are often heard concerning failure of memory. This is referable more to the fact that women at this time first appreciate the physiological diminution of memory, while, as a matter of fact, memory and the powers of observation have been undergoing a gradual diminution for very many previous years. It is exactly the same as is the case in the gradual loss of accommodation power of the eye for near objects, which from childhood on progressively diminishes. The realization of old age, as also of failure of memory, comes when spectacles and the memorandum book become necessities. Between the above-mentioned mental changes at the menopause and the psychoses belonging to this period of life, all possible intermediate stages appear.

The tendency to corpulence at the climacterium is noteworthy; moreover, the accumulation of fat is characterized by a localization to parts of the body other than those affected during the time of fullest vigor. The figure changes to that of an old woman, but this is brought about less through a change in the osseous system, therefore, in the attitude of body, than through the accumulation of fatty tissue.

The changes in the heart and circulatory system are difficult to understand. It is a well-recognized fact that during the menopause many women begin to complain of heart trouble. Clément has described the "cardiopathie de la menopause," and Kisch also has called attention to it. There is seen, for the most part, a certain enlargement of the heart and a cardiac arrhythmia of the type of the extrasysto e. Extrasystolic arrhythmias are frequently the sign of an inequality between the strength of the heart and the resistance to be overcome. An examination of the blood pressure frequently showed me in such cases a hypertension such as we should scarcely expect in women. Readings of 180 to 200 mm. of mercury (Riva-Rocci apparatus) are not at all unusual in such cases. We will hardly err if we ascribe this elevated blood pressure to arteriosclerotic processes. Arteriosclerosis of women may, for the most part, be attributed to causes other than is that of men. It seems much more frequent in women who have had children, and especially in those who have brought children into the world a number of times, than in unmarried or sterile women. Probably it has a certain relationship to the cardiovascular conditions of pregnancy

already referred to. The cardiac disturbances of the climacterium, which can finally develop the picture of severe heart-muscle insufficiency, occur certainly much more often in fat than in thin women, and the functional weakness of the heart has a certain relation to the general loss of muscular power, which in the corpulent generally can attain a high grade, but does so especially in fat women at the time of the menopause.

While the process of the menopause under normal conditions occupies a period of from one to three years, it may occur very quickly if disease of the sexual apparatus makes the complete operative removal of the ovaries necessary. In this postoperative "climacterium præcox" we see all the characteristic appearances of the menopause occur much more violently: the congestions of the head and other vasomotor signs, palpitation of the heart, the tendency to fat deposits leading to the characteristic posture of the old woman's figure, the loss of physical and mental energy, and above all the signs of psychic disturbances and depression.

I have seen several cases in which total extirpation of the reproductive organs during the twentieth or thirtieth year produced extraordinary consequences on the mentality and the entire personality, and blighted blooming, promising careers. Careful operators, in order to lessen the unfavorable results of the "climacterium præcox," seek to leave behind a small piece of the ovary. Removal of the uterus alone seems not to call forth these severe sequels, but a number of my cases seem to indicate that the untoward results reach an especially high grade when, in addition to the ovaries, the uterus is totally removed.

It is well known that a sterile marriage can bring with it serious mental disturbances to the wife. Indeed, this concerns not only those women in whom sterility has occurred through disease of the uterus and adnexa, but also in those in whom the cause of the sterility is to be sought in the person of the husband. Finally, it also holds true for the women with underdeveloped uterus and sexual organs, who often are conspicuously slender and tall, and whose pelves resemble more the type of the male pelvis. If, in the sterile woman, the desire for a child is very keen, the occurrence of every menstruation brings a new disappointment, and each accidental delay of the period arouses a false hope whose unfulfilment is then that much more disappointing. This continual change between hope and disillusionment not infrequently results in a shattering of the psychic well-being, which at first expresses itself in abnormal susceptibility and irritability, but finally in all the possible symptoms of hysteria. When the husband, as so frequently happens in sterile marriages, regards his wife with particular affection, there then often develops a condition of affairs in which the wife seems like the child, indeed, the spoiled child, of the husband. Only when the menopause banishes the last hope of issue comes peace.

II. Diseases of the female reproductive organs can give rise in the most varied ways to pathological processes in other internal organs. I shall not at this time touch upon their relation to the nervous system, and hysteria in particular, a theme which has been discussed many times and of which our conception has undergone many changes.

Disturbances of the function of the bowels are to be mentioned among the most frequent sequels of diseases of the uterus and adnexa. Constipation is the rule. It may be caused mechanically, but is also often encountered when pressure on the sigmoid or rectum does not exist. Further, this constipation can give rise to a whole train of resulting symptoms.

We see especially frequently mucous colitis in association with diseases of the reproductive organs. Typical mucous colitis is a condition which belongs almost exclusively to the female sex. Indeed, it is found chiefly in those women who present a neuropathic tendency and the most varied symptoms of a nervous character. Those who carefully investigate these cases will be surprised how frequently diseases of the uterus and adnexa may be recognized with it. It is hardly possible to give an explanation for this relationship. All cases of mucous colitis are certainly not to be brought into etiological relationship with the reproductive organs. Many of them may occur as the result of constitutional anomaly, by means of abnormal mucous secretion and spasm of non-striated muscular fibers, just as bronchial asthma, which is characterized by an excessive migration of the eosinophilic leukocytes to the diseased mucous membrane.

We see that myoma of the uterus is accompanied, with exceptional frequency, by evidences of disease in other organs. The danger attendant upon the "myoma heart" was first recognized by the surgeons. In these cases, in which, after a successful myomectomy, sudden heart failure occurs, there is usually found a markedly soft and flabby heart. This condition of the heart muscle must be regarded as the result of frequent and profuse uterine hemorrhages. During life, however, disturbances of cardiac action are also observed in those cases of myoma in which the loss of blood throughout has not been excessive, and in which the blood examination itself reveals no noteworthy impoverishment of the blood corpuscles and hemoglobin. The relation of myomas to the diseased condition of the myocardium cannot be explained by the anemia alone. Furthermore, the mechanical pressure of the uterine tumor cannot be held responsible for this condition. To give a satisfactory explanation of the relation between myomas and heart disease is at present impossible.

The relation between myomas and goitre is equally obscure For a physician whose field of activity lies in a goitre country it is naturally difficult to say whether this relationship is only accidental,

or whether it can also be claimed as applying to other lands. However, it has also been noticed by other authors, as for example by H. W. Freud and Fischer. In Munich it is so common that I have made it a rule to examine all women with thyroid enlargement for myomas, and vice versa.

The outspoken picture of hyperthyroidism is often associated with abnormal enlargement of the heart and a quickened irregular pulse. Therefore, in a considerable number of cases it is difficult to decide whether it is better first to operate upon the goitre or the myoma, or whether, in consequence of the danger from the struma and heart, a myomectomy should be permitted at all. From the experience of gynecologists it has been repeatedly proved that a myomectomy exercises a avorable influence upon both the heart and the thyroid.

One also sees, now and then, that disease of the adnexa can give rise to disturbances of the heart. I have seen cases of severe gonorrhœal pelvic inflammation in which there has occurred, almost regularly with every menstruation, arrhythmia of the heart, excessive rapidity of the pulse, and even true delirium cordis. These women, at their menstrual periods, find themselves in a condition of pitiable cardiac weakness, which is only slightly influenced by strychnine and heart stimulants. With improvement in the diseased condition of the adnexa, or with the advent of the climacterium, this condition may completely disappear.

The frequent relationship between disease of the adnexa, as well as inflammation and adhesions in small pelves, to the nervous system is well known. Let me caution you that the resulting pain, weakness, and paralysis of the lower half of the body is always to be regarded as reflex or as functional. A thorough examination often reveals that, due to inflammation and adhesions in the pelvis, there has occurred an injury, a pressure palsy, or a neuritis of the nerves passing through the pelvis. For the woman whose constant complaints have been regarded as hysterical and been looked upon with indifference, it is always a real satisfaction when the establishment of an organic lesion furnishes a certain amount of justification.

The relationship of gynecological diseases to the organic diseases of the peripheral nerves and central nervous system has also been admirably considered by Rudolph von Höslin.

III. We now come to the diseases of other organs in which a certain relationship to the female reproductive organs is recognizable. In this connection first to be mentioned are diseases of the kidneys and urinary tract.

The relationship of kidney disease, in its strict sense, to the female sexual organs may be twofold. In the first place, pregnancy can lead to the kidney of pregnancy. The latter is found in the vast majority of all cases of eclampsia; at all events it stands in the closest

relation to it, even if eclampsia may not be considered as alone the result of the kidney of pregnancy.

The high albumin content and the large number of casts which may be observed in this disease prove that a severe affection of the kidney tissue exists. The macroscopic appearance of the kidney, with the high grade of fatty degeneration of the parenchyma also warrants this interpretation. However, the microscopic examination proves that the epithelium, in spite of the marked infiltration with fat droplets, has undergone no true necrosis, that the nuclei are preserved, and that the glomeruli show no change worthy of mention.

The clinical course shows that a quick recovery is established soon after the discharge of the product of conception, and that after a few days the urine may show a completely normal condition. The lesions of the kidney tissue, notwithstanding the striking associated phenomena, are not of a serious nature, or, at least, are amenable to quick repair. Nevertheless, to conclude, from the microscopic appearance of stained preparations, that the functional disturbance of the kidney of pregnancy is unimportant, is at variance with the suppression of urine at the height of the disease and with the severity of the symptoms and the danger to life, as well as with the frequency with which a premature termination of pregnancy occurs. Unfortunately, I do not know how the blood pressure acts in the nephritis of pregnancy and in eclampsia.

The kidney of pregnancy has been rightly considered the result of an intoxication from the fœtal site. However, it is yet to be determined whether the products of the metabolism of the child or a syncytiotoxin furnish the cause.

On the other hand, pregnancy can occur in a woman who previously has suffered with nephritis. The nephritis may light up in the course of the pregnancy, and, indeed, this is the rule. Uremia may occur, which is with difficulty distinguished from eclampsia, and thereby may threaten the life of the mother. In such cases, in which the materal life is preserved, it now and then becomes manifest that, as a result of pregnancy, the nephritis has suffered a further and permanent aggravation.

Pregnancy, however, by no means always exerts such an unfavorable and dangerous influence on a preëxisting nephritis, and the danger of uremia or eclampsia is in no way so great as many suppose. It is not unusual for a woman who has chronic nephritis to undergo many pregnancies without special harm, but the life of the child in all these cases is in the greatest danger. The product of conception almost always, sooner or later, dies and is discharged. The majority of nephritic women experience the misfortune that in spite of repeated conceptions they are unable to bring a living child into the world, a fact which seems to warrant prohibition of marriage in chronic nephritics. The inability of the kidneys completely to eliminate from the body the waste products of metabolism seems more dangerous to the child than to the mother.

It is recognized that inflammation of the bladder, and especially of the pelvis of the kidney, is extremely frequent as the result of pregnancy and disease of the female reproductive organs. Indeed, it is often the difficulty in emptying the bladder which, through the resulting retention, induces undue distention of the bladder, ureters, and pelves of the kidneys, that favors infection. As a rule, we see that a bacterial infection can very easily take place, especially at that place where stasis of the secretions occurs. This applies to the urinary tract as well as to the stomach, the intestines, the gall-bladder, and the bronchi. The bacterial infection of the bladder, the ureters, and the pelves of the kidneys in many cases certainly occurs from the urethera. In support of this, facts indicate that in woman cystitis and pyelitis occur disproportionately more frequently than in man, whose urethra is longer and whose bladder is more tightly closed.

However, the possibility must also be reckoned with that infection of the urinary tract can also occur directly from the adjacent intestines and through the blood and lymph. In support of this possibility is the fact that in many cases the pelvis of the kidney apparently is first involved and that the bladder shares secondarily in the inflammation. Further, it is to be observed that these pyelitides and cystitides show with overwhelming frequency, as the single infectious agent, Bacillus coli communis, the normal occupant of the intestinal mucosa. Also in other cases, in which later Proteus vulgaris, the causative factor of ammoniacal urine fermentation, or other bacteria are found, the presence of Bacillus coli communis is often established first.

Finally, pyelitis occurs chiefly in those individuals who suffer from obstinate constipation. It has been shown that in stagnation of the intestinal contents the bowel wall becomes permeable for bacteria. From the relationship between constipation and pyelitis it follows that the therapy of pyelitis only offers the prospect of success when it is efficient in overcoming the constipation.

The pyelitis begins for the most part acutely, with sharp pain on the side of the affected kidney, and usually with considerable fever. The urine is often bloody and shows almost constantly, by a considerable quantity of albumin and casts, that the kidney is involved. The number of bacteria in the urine is very great. A number of bacteria present in urine removed from a sterile bladder need not always be the sign of a cystitis or pyelitis. As is well known, this occurs in infectious diseases due to bacteria of various kinds and from various parts of the body, in erysipelas, angina, endocarditis, typhoid fever, mastitis, and phlegmons, and sometimes from the secretion of the infectious agent through the kidney. But, this excretion of bacteria through the urine does not tend to produce inflammatory changes in the urinary tract. It does not lead to an increased number of leukocytes in the urine and purulent cloudiness of the urine,

and commonly disappears within a short time. As opposed to this bacterial excretion in infectious diseases, the bacterial infection in pyelitis proves to be extraordinarily obstinate. It withstands all antiseptics, even urotropin, and I have yet to see the urine after pyelitis become absolutely bacteria-free. The inflammatory phenomena, however, the albumin and leukocytes in the urine diminish in the course of a few weeks after careful treatment, and finally the picture of chronic bacteremia results. In that condition bacteria, indeed, especially the colon bacilli, are still present in numbers, but give no more indications of the signs of inflammation in the region of the pelves of the kidneys or bladder. There must be established a form of tolerance or immunization of the mucous membrane to the particular bacteria.

If, however, in such cases, there occurs at any time an obstruction along the urinary tract, the inflammatory processes soon flare up again; once more pain, fever, and marked leukocytosis occur, and the urine again shows a sediment of pus. It is for this reason that during pregnancy, in chronic infection of the urinary system, there is always the danger of again lighting up a pyelitis, and the damming up of pus in the pelvis of the kidney leads to pyonephrosis. Pregnancy, therefore, can give rise, through stagnation along the urinary tract and through constipation, not only to the primary origin of infectious pyelitis, but it may also induce a recurrence of the process in an already infected urinary tract. Pus in the renal pelvis during gestation may lead to quite serious symptoms and protracted febrile conditions. In many cases the condition becomes so serious that assistance of an operative nature must be sought.

Opening of the renal pelvis, for example in pyonephrosis, leads to a continuous discharge of pus from the wound, and intolerable annoyances from such a fistulous formation result. An extirpation of the kidney itself is only justified in those cases in which the entire kidney is destroyed by pus and when the other kidney is healthy. One will not lightly decide upon this operation. It is much more preferable to terminate pregnancy and save the life of the mother.

In the pyonephrosis of pregnancy the prognosis is favorable in so much as the obstruction is produced by a process of transitory nature. One can see the end and, in imminent danger, at any time terminate pregnancy. The prognosis of urine stagnation is worse in many gynecological diseases, in which neoplasms and dense adhesions in the pelvis produce compression of one or both ureters. In such cases, should an infection of the pelvis of the kidney occur, thus leading to pyonephrosis, in many cases nothing can be done but extirpation of the kidney, provided the process is unilateral.

If, on the other hand, ureteral compression involves both sides, the woman will lapse into a chronic illness, and after marked

febrile manifestations will finally succumb with uremia. It has been denied that blocking of the ureters can lead to true uremia. As a matter of fact, one sees that an acute blocking of both ureters usually does not produce the typical picture of uremia; the patients succumb rather to a progressive asthenia, as Ascoli especially has emphasized. In chronic ureteral constrictions, on the other hand, one notes, in the course of time, typical blood pressure elevations up to 180 to 200 mm.; indeed, as I once saw, up as far as 300 mm. mercury. Hypertrophy of the left and also of the right ventricle may be recognized; headache, vomiting, and, indeed, severe uremic attacks may be observed. Only a longer time is necessary to bring these uremic conditions to full development. In one such case, in which both ureters were compressed by a malignant growth of the uterus and bilateral hydronephrosis existed, I could establish, in association with a considerable blood-pressure elevation recognizable during life, an hypertrophy of the left ventricle, as shown by post-mortem examination. The kidney tissue was involved to a marked degree, there was present a slight increase, and here and there also a certain infiltration, of the interstitial tissue. The uriniferous tubules were compressed and displaced as a result of the pressure of the hydronephrosis, but a vast majority of the glomeruli showed no change. This case proves that blood pressure elevation and heart hypertrophy can occur without any essential anatomical damage to the glomeruli.

In case of an infectious pyelitis, the pelvis of the kidney is infected by inflammation-producing organisms; therefore this process is never unimportant for the kidney itself. Indeed, only in the first acute beginning of such a pyelitis does the urine tend to contain a large amount of albumin, casts, and blood casts in greater numbers. The blood pressure in acute pyelitis always remains normal. If, however, the pyelitis lasts a year, not infrequently the albumin content gradually again becomes greater than corresponds to the coincidently diminishing suppuration. Vascular hypertension and hypertrophy of the heart gradually develop, and finally, the picture of a chronically progressing contracted kidney results.

Fieder has described a symptom-complex, designated by him, as ovulation fever (*Ovulationsfieber*), in which at the time of menstruation, there appear a fever of short duration, sometimes slight and sometimes again high. I, too, have seen such cases: women, who in the interim give the impression of complete health, become ill at the time of menstruation, with febrile phenomena of considerable intensity. They have complete loss of appetite and coated tongue, with decidedly marked constitutional symptoms, and a certain pain may be elicited by pressure above the symphysis. Sometimes such febrile movements occur exactly midway between two menstruations, at the time when many women feel the so-called middle pain (*Mittelschmerz*). The association of these febrile movements of

only two or three days duration with menstruation was unmistakable. Concerning this, it has been thought that this ovulation fever is the result of the physiological incident of the ruptured follicle in the ovary and the associated phenomena of hyperemia. I prefer to consider that these febrile manifestations occur only in those cases in which a latent disease of the genitalia previously exists, which either depends upon a gonorrhœal basis, or exists in connection with some other form of infection, for example, puerperal infection. I surmise that through hyperemia incident to menstruation this latent focus of infection again lights up. The tenderness above the symphysis or slight pain and swelling of the adnexa seems to me to confirm this explanation. Upon more careful examination my cases showed that there was present every time a chronic infection of the urinary tract, as a pyelitis, and this, indeed, acted like an infection by either colon bacillii or proteus. It could also be established that at the time of the attacks of fever a spontaneous lumbar pain was sometimes complained of, or that bimanual palpation of the kidney region caused pain. Although I do not entirely ignore the first-mentioned possibility, it seems that the last-named observation points to the fact that a pyelitis underlies many cases of ovulation fever, and that this pyelitis, in connection with menstruation, undergoes an aggravation similar to that which has already been considered in connection with pregnancy. Whether menstrual processes can really lead to fever and the phenomena of sickness, if the genital organs and the urinary tract are absolutely normal and free from infection, I must leave to the gynecologists to determine.

The bile passages show relations to the female reproductive organs quite like those we have discussed in connection with the urinary tract. It is recognized that cholangitis, cholecysitis, and gallstones occur three to five times more frequently in women than in men. It is certain that intestinal sluggishness is responsible above everything else for the conditions of congestion and infection of the biliary tract. This is perhaps the reason why we find gallstone colic in association with diseases of the female genitalia.

Above all else, pregnancy is undeniably associated with gallstones. I have repeatedly seen gallstone conditions in pregnant women and still more frequently in the course of the puerperium and in the succeeding weeks. Many times patients have come to me, in whom during the course of the puerperium an attack of fever and severe abdominal pain have given rise to the suspicion of a puerperal infection, but in which the further course of the disease—localization of the pain to the region of the gall-bladder radiating to the right shoulder, as well as the occurrence of slight jaundice, and a distinct urobilin reaction in the urine—made certain the diagnosis of gall-bladder disease. If one elicits accurate histories from women who for years have suffered with gallstone colic, in many cases he can convince himself that the first attack of colic, which usually was first

regarded as pain in the stomach, occurred in these people after a puerperium. Married women who have had many children are, at all events, much more frequently the subjects of gallstones than the unmarried.

Appendicitis also has a relationship to diseases of the female genital tract. I have repeatedly seen acute appendicitis, the initial attack as well as recurrences, occur at the time of menstruation. It is often difficult to differentiate between appendicitis and an acute inflammation of the adnexa. Often in an outspoken appendicitis the adnexa show a certain participation, since they appear to be the seat of inflammatory swelling and pain. In the further course of the disease the adnexa may be pulled up and fixed by means of adhesions with the inflammatory process in the appendix. In disease of the adnexa in combination with appendicitis one rarely makes a mistake if the appendicitis be regarded as primary and is treated as such. If appendicitis has existed and has left relics behind, with every menstrual period a fresh attack of pain may occur. Pregnancy may also influence detrimentally an incompletely healed appendicitis. I remember one case in which continued appendiceal pain led to an examination of the pelvic organs, whereupon the presence of beginning pregnancy was proved. In those cases in which the appendix has been removed because of appendicitis, inflammations, adhesions, stitch and stump abscesses of the female reproductive organs may occur in sympathy, or disease of the adnexa and painful pregnancy may be produced at the site of the old operative scar.

Just as the appendix is, so also may the pelvic organs be sympathetically involved by inflammation which originates at the sigmoid. Sigmoiditis and perisigmoiditis are by no means as rare as was formerly believed. They stand in etiological relationship to many cases with persistent constipation, and the resulting adhesions may give rise to kinks of the intestines, obstinate constipation, and indeed to ileus. Perisigmoid adhesions may claim as their sequels dragging on the bladder, pain upon overfilling of the bladder, as well as displacements of the uterus and adnexa. It has been shown that sometimes chronic constipation may give rise to inflammatory conditions in Douglas' pouch, and thereby to disturbances in the female genital area. This periproctitis, which, however, is caused not only by chronic obstruction, but also by all sorts of other diseased conditions of the lowest part of the bowel, stands in the closest relation to perisigmoiditis.

It still remains, however, to take up the relation of the female genital organs to the constitutional and infections diseases, but out of this vast field only two chief headings shall be dealt with—diabetes and tuberculosis. It is the rule that pregnancy and the puerperium are excessively fatal in diabetic women. I have seen and observed exceptions to this rule, that is, that women, who suffered with well-

marked glycosuria have passed through several labors without injury to their health. Such observations, however, must not mislead one from the principle that in the presence of diabetes marriage must be urgently opposed.

As in many other infectious diseases, for example, typhoid fever, smallpox, and pneumonia, it follows in tuberculosis that pregnancy and the puerperium exert in general a deleterious influence. A previously latent or at least favorably progressing tuberculosis may during the course of pregnancy experience a rapid spread and aggravation, and not infrequently in the course of the puerperium a fatal termination occurs. I have never observed that pregnancy had a favorable influence on tuberculosis, as has been stated by some physicians. The unfavorable effect which pregnancy, as a rule, exercises on tuberculosis is one of the most significant examples of the importance of predisposition, that is, of the general state of nutrition, in the development of this disease. Indeed, here it is an acquired and temporary alteration in the nutrition of the organism that smooths the way for an acute increase of the disease.

The numerous observations which we make concerning the influence of pregnancy on tuberculosis obligate every conscientious physician to oppose most earnestly the marriage of girls suffering with tuberculosis. But what is the result of this medical advice? Of the many young women with incipient tuberculosis who have consulted me in regard to the advisability of getting married, and whom I always most emphatically warned against it, *all* have married, and, with a single exception, all have died within a few years. This exception became pregnant on her wedding journey, and shortly thereafter had a severe hemoptysis. An induced abortion brought the fever and the spread of the disease to a standstill. Not only in this, but in many other cases of beginning tuberculosis, have I seen an early interruption of pregnancy favorably influence the further course of the disease.

The foregoing explanations may, notwithstanding their incompleteness, afford a picture of how numerous are the relations between internal medicine and diseased conditions in the female reproductive organs. They should emphasize how important it is for the internist, and especially for the general practitioner, to turn his attention to the gynecological condition, and in suitable cases to seek the advice of the gynecologist. On the other hand, with justice we can expect the gynecologists to direct their attention, more than they have heretofore, to medical disorders, and in doubtful cases to secure the advice of the internist.

THE SPECIFIC TREATMENT OF TYPHOID FEVER.

By Victor C. Vaughan, M.D.,
PROFESSOR OF HYGIENE IN THE UNIVERSITY OF MICHIGAN, ANN ARBOR, MICHIGAN.

It is the purpose of this paper to discuss general principles rather than to go into details. I wish to inquire into the probabilities of the discovery of a specific treatment for typhoid fever and what the nature of such treatment is likely to be, and how much we may expect from it. It seems to me that enough has been done to convince us that no antitoxin, comparable to that which we have for the treatment of diphtheria, is likely to be found for typhoid fever. Diphtheria is so essentially different from typhoid fever in the nature of the infection that to draw conclusions from the one and try to apply them to the other seems wholly without warrant. In the former the bacillus grows on a mucous surface, developing a chemical poison which is absorbed into the circulation and which induces the systemic symptoms of the disease and causes death. In typhoid fever the bacillus first finds its way into the interior of the body and finally into the blood. One is, strictly speaking, apart from its local action, an intoxication; the other is a true systemic infection. In diphtheria the bacillus is the producer of the poison; in typhoid fever the bacillus is the poison. The poison of diphtheria reaches the blood as a soluble, chemical body; the poison of typhoid fever reaches the blood as a living, multiplying cell. The poison of diphtheria is a soluble toxin; that of typhoid fever is an integral part of the bacterial cell, and if our definition of a toxin is a poison that may be used to generate an antibody to itself, the active agent in the typhoid bacillus is not a toxin, because there is not the slightest evidence that in any animal it elaborates an antibody.

There is no satisfactory evidence that the typhoid bacillus produces a soluble poison. It may be true, as has been asserted by some, that old cultures of the typhoid bacillus, after the removal of the bacterial cells by filtration through porcelain, are slightly poisonous, but any feeble action that may be shown by such filtrates is easily accounted for by the autolytic changes that go on slowly in all cells and, in fact, in all organic matter. No one has ever been able to produce an antibody by treating animals with such filtrates or any other culture of the typhoid bacillus, living or dead, young or old, filtered or unfiltered.

It seems to me that the time has come for us to recognize that the mechanism of immunity is not the same in all infections and intoxications. I think that there is already sufficient ground to justify us in holding that there are at least three forms of immunity, and these I will briefly designate as follows: (1) *Antitoxin Immunity.* The poisons to which this form of immunity has been secured

are the venom of serpents, vegetable poisons, such as ricin and abrin, and the toxins of Bacillus diphtheriæ, Bacillus tetani, and Bacillus botulinus; possibly others may be added to the list in the future. These poisons apparently constitute a distinct group, and they resemble enzymes in the following striking particulars: (*a*) in aqueous solution they are destroyed by a temperature of 100° or less; (*b*) they are active in solutions so dilute that they do not respond to the three most characteristic proteid color reactions, the biuret, Millon, and Molisch tests; (*c*) animals treated with successive doses at proper intervals develop antibodies; (*d*) their effects are not immediately manifest, but develop only after a period of time. For the present, at least, Ehrlich's side-chain theory must be regarded as the most satisfactory explanation of this form of immunity. There is no proof so far that either phagocytic activity or proteid cleavage has any concern in the production of this form of immunity. (2) *Phagocytic Immunity.* This form of immunity has been best studied with the cocci, and it has been shown experimentally that with virulent or slightly virulent strains phagocytic activity may be markedly increased, but that with highly virulent strains it is difficult to demonstrate increased efficiency in the destruction of bacteria by the phagocytes. (3) *Lytic Immunity.* This is frequently designated as bactericidal or bacteriolytic immunity, but there are the following grave objections to the employment of either of these terms: (*a*) bacterial proteids are not the only proteids that may be, and are, split up in the animal body. Most foreign proteids, when introduced directly into the circulation and without previous subjection to the digestive juices, undergo specific proteolysis, and this is true whether these proteids are living or dead. (*b*) The cleavage of poisons in the body is probably not confined to those of proteid composition. (*c*) The term bactericidal is inappropriate, because the bacteria may be so altered chemically that they are robbed in part or wholly of their harmful properties, and still are not killed. Examples of the persistence of specific bacteria in the body after recovery from the disease are well known, and immunity to disease may co-exist with the specific bacterium of that disease still living in the body. The bacterial proteid owes its poisonous action to its molecular structure, and this may be so modified as to render the organism a comparatively harmless guest without destroying its life. (*d*) The term bacteriolysis is certainly inappropriate, first, because all these poisons are not bacteria, and the term implies that the bacterial cell is destroyed; and we have just seen that this does not happen in all cases. In view of the facts here briefly considered, I prefer the word "lytic" to designate this form of immunity; however, I am not altogether satisfied with this term, and hope that some one will soon suggest a better.

There is no antitoxin for the typhoid poison; phagocytic action certainly is not a marked factor in the natural recovery from this

disease, and it is my purpose to see what we can make out of lytic action in the study of the nature, progress, and recession of typhoid fever.

It is probable that in some diseases two of these immunizing or protective factors may combine in aiding the animal body in its contest with infection. This seems to be the case in tuberculosis, for instance, in which phagocytic and lytic immunity both are concerned, with the latter playing the more important role. Future studies may show a closer relation between phagocytic and lytic protection than can be demonstrated at present, but both of these differ so radically from antitoxin immunity that to try to explain them by the same theory seems to be without justification. Such passive immunity as we secure when we treat a diphtheritic child with specific antitoxic serum is wholly without any parallel in typhoid fever, colon infection, tuberculosis, or pneumonia. In the former the cellular activities of the child are not awakened at all; its circulatory system may be compared to a large, branched test-tube, into one arm of which the toxin produced by the bacillus growing in the pharynx is poured, while into another arm the antibody or neutralizing agent is introduced. In short, the treatment of diphtheria with the antitoxin is in essence an experiment *in vitro*, with only this difference, that if the poison is not neutralized by the antidote promptly it may act upon certain cells in the child's body and may cause death, and just to the extent that it is not neutralized it does cause sickness. In the other diseases mentioned there is no such soluble poison, and we possess no such antidote. The poison is a particulate, living multiplying cell, and it can be destroyed only through the activity of the body cells, and when the invading cell is destroyed its poisonous constituent can be neutralized only through the activity of the body cells.

For some years my students and I have been engaged in the study of the so-called endotoxins, or, as I prefer to designate them, the proteid poisons. We have shown that all the true proteids with which we have worked can be split by chemical agents into poisonous and non-poisonous groups. We have been able to accomplish this by extracting the proteid body at 78° with a 2 per cent. solution of sodium hydroxide in absolute alcohol. This causes slow hydrolysis, by means of which cleavage of the proteid molecule is secured. When the process is properly carried out the separation of the poisonous and non-poisonous constitutents is fairly satisfactory. The method is certainly crude compared with the like process as it takes place in the animal body, and, as we have elsewhere stated, much of the poisonous group is destroyed by our method, but there is enough left to enable us to investigate its properties. The proteid molecule, whether it be of egg-white or of the typhoid bacillus, is made up of groups, consisting for the most part of the mono-amino and di-amino acids, combined with one another, with phosphorus,

and with carbohydrate. The exact manner of these combinations, even in the simplest proteids, is not yet known. We have obtained the cellular substance of the typhoid bacillus and of other bacteria in large amount, and have shown by splitting them up that they are, in their essential parts at least, true proteids, just as much so as are egg albumin and serum globulin. For our present purpose it is well to regard the typhoid bacillus as a living proteid, capable of growth and multiplication, but chemically nothing more than a proteid.

It will be best to state briefly some of the properties of the products obtained by splitting up the proteid molecule with dilute sodium hydroxide in absolute alcohol. As has been stated, this method breaks the complex body into two simpler parts, one of which contains all the poison. The poisonous portion is freely soluble in absolute alcohol, while the non-poisonous portion is wholly insoluble in this menstruum. Indeed, this is the chief reason for using an alcoholic rather than an aqueous solution of dilute alkali in effecting the cleavage. When water is used as the menstruum, both portions being soluble in this, separation is obtained with difficulty and imperfectly. That the cleavage has followed a definite line in the molecular structure is shown by the following: (*a*) the poison contains no phosphorus, (*b*) the poison contains no carbohydrate, and (*c*) the poison contains the greater part of the aromatic radical. These facts show that the separation is a chemical one, a true molecular cleavage, and not a mere disintegration. The splitting process has followed a definite structural line; otherwise, the phosphorus and the carbohydrate could not all be in one of the products. In other words, the cleavage is such as one might expect to obtain by the action of a ferment. If it be objected that I have no right to compare the effect of so gross an agent as an alcoholic solution of sodium hydroxide with so delicate a one as an enzyme, I need only inquire in return whether or not there is any difference between the tyrosin obtained by the digestion of meat with the pancreatic juice and that obtained from the same meat by splitting it up with 30 per cent. sulphuric acid? Besides, the trypsin acts at the temperature of the animal body, while the meat is boiled for hours with 30 per cent. sulphuric acid, and yet both processes yield the same tyrosin. Compared with the sulphuric acid used in preparing tyrosin, our dilute solution of sodium hydroxide in absolute alcohol is mild indeed. It is characteristic of ferments that they induce at relatively low temperatures chemical reactions that can otherwise be brought about only with powerful chemicals at relatively high temperatures. Chemists are fond of comparing the complicated structure of the proteid molecule to that of a house of cards, and this is a fit comparison. Now, when the house of cards is blown down, whether it be by the breath of the child that has built it or by a blast of wind, it is blown into cards in each case—nothing more. The greater force

may scatter the cards more widely, and it may even twist and tear some of the individual cards, but, on the whole, the house is broken up into its constitutent parts whether the disrupting force be the breath of the child or a blast of wind. I dwell upon this point because I shall attempt later to show that by our method we have split up the typhoid bacillus, obtaining not only the true endotoxin, but its specific antigen. Quantitatively I not only admit, but I know, that our method is crude, and that the amount of poison obtained from a given number of bacilli is less than that liberated in the animal body, but qualitatively the results are the same.

If we are to study typhoid fever satisfactorily, it will be necessary to go into some detail concerning the products obtained by cleavage of the cellular substance of the typhoid bacillus. In the first place, I will briefly state the method of obtaining typhoid bacilli in large amount. This organism is grown in incubating tanks 10 feet long and 2 feet wide, and with six of these tanks in operation we are able to obtain abundant growths. When the growths have reached maturity they are detached from the subjacent agar, drawn into proper receivers, washed with physiological salt solution, then placed in Soxhlet's apparatus and thoroughly extracted first with alcohol and then with ether. The germ substance thus obtained is finely ground, passed through a fine-meshed sieve, then split up with the alcoholic solution of sodium hydroxide, as already stated.

The poisonous portion is freely soluble in alcohol and in water, more freely in the former than in the latter. It is also soluble in methylic alcohol, but is insoluble in chloroform, benzene, and ether. From its alcoholic solution it is precipitated by ether. Its aqueous solutions respond to the biuret and Millon tests for proteids, and at present we must regard the poison as still a proteid, but, of course, of much simpler structure than the bacterial substance from which it has been obtained. When the poison is split up with 30 per cent. sulphuric acid it yields mono-amino and di-amino acids, tyrosin being present in large amounts. The poisonous action of this body is probably due to the aromatic radical which it contains so abundantly, and to which its ready response to the Millon test is due. So far we have split up some twenty-five proteid bodies, bacterial, vegetable, and animal, and we have found no true proteid that has not yielded a poisonous group. The albuminoid gelatin contains no poison, and it contains no aromatic group, or contains such a group only in minute trace, as is shown by its failure to respond to the Millon test. This is additional proof that the aromatic radical constitutes the poisonous group, or is contained in it. In this connection, Wells[1] has found that animals are not sensitized by gelatin as they are by the true proteids. This is what we should expect, since gelatin does not contain a poisonous group. As Wheeler and

[1] Jour. Amer. Med. Assoc., February 15, 1908.

I have found, and as has been confirmed by Nicolle and Abt,[2] Witte's pepton does contain a poison, but the French scientists have found that Defresne's pepton does not. It would be interesting to know whether the latter is made from gelatin or from a true proteid.

The effect of the isolated typhoid poison on animals is identical with that of any other proteid poison. While the proteid poisons are probably not identical chemically, they are identical in their effects upon animals, and if the white of egg could be introduced into the blood and could grow or increase in amount after its introduction, it would cause disease and death much as the typhoid bacillus does. The latter is a living, growing, multiplying proteid, and it is because it can live, grow, and multiply in the body of man that it is able to induce disease.

The effect on animals of the free poison obtained by splitting up the typhoid bacillus after the manner stated is of much interest. It is the same as that of all the proteid poisons with which we have worked, and I believe that in certain diseases, notably in colon and typhoid infection and in tuberculosis, possibly in many other diseases as well, the poison is practically the same. The specificity of these diseases does not lie in the poisons produced in them, but in the non-poisonous constituents of their respective bacteria. When the free typhoid poison is administered to a rabbit or guinea-pig by the mouth there is no recognizable effect. This may be due either to destruction of the poison by the digestive juices, or to the slowness with which it is absorbed. When the poison is introduced into a collodion sac and this is placed in the abdominal cavity of a rabbit, there is no detectable effect. In this case the failure to induce reaction is best explained by the slowness with which the poison is absorbed, the comparative insusceptibility of the animal, and the difficulty that we have of recognizing anything but relatively abrupt effects upon animals. That man is much more susceptible to this poison than laboratory animals is shown by the fact that when we rub up the crude typhoid poison in a mortar, if the mouth and nose of the operator be not protected by a mask, the operator has frequently shown evidence of poisoning. The first thing noticed is an irritation of the nasal mucous membrane and a huskiness of the voice; this is followed by a feeling of depression and malaise, with chilly sensations, after which the temperature has been found as high as 102°. Rarely nausea and vomiting have resulted. After a period of discomfort of from six to ten hours, with pain in the joints, complete recovery follows.

When a fatal dose of the free poison is administered to a guinea-pig subcutaneously or intra-abdominally there are three distinct stages in the symptoms developed. The first is one of peripheral irritation characterized by restlessness and itching. The animal

[2] Annales de l'Institut Pasteur, February, 1908.

scratches itself quite violently, not especially the point where the injection was made, but every part that can be reached with the foot. During the second stage the animal lies on its side or abdomen, quite limp; there is partial paralysis, most marked in the posterior extremities. The last or convulsive stage is characterized by more or less violent clonic convulsions, due to, and quite characteristic of, failure of respiration. The heart usually continues to beat quite regularly for some minutes after respiration has ceased. When the dose is administered intra-abdominally the quantity required to kill is reduced one-half and the symptoms follow one another more rapidly. In intravenous injection death occurs so quickly that a detailed study of the symptoms is quite impossible. Evidently the poison destroys life by its effect upon the cells of the respiratory centre. When introduced subcutaneously some of it is fixed apparently by the local cells, and the rest of it is slower in reaching the brain. Besredka[3] has found that ether narcosis prevents the fatal action of a second dose of horse-serum in animals sensitized to this fluid, and we find that the same means may save the life of an animal treated with a more than lethal dose of the free poison. A guinea-pig was given intra-abdominally 150 mg. (two and one-half times the lethal dose) of the free poison, and immediately thereafter was deeply narcotized with ether and held in this state for twenty minutes, and then allowed to recover. This animal showed no symptoms of the poison, while of two controls that received the same dose of the poison one died within five, and the other within seven minutes. It seems that the ether prevents the combination of the poison with the cells of the respiratory centre, and that the poison in the mean time is fixed by other cells, the continued function of which is not so directly essential to the continuance of life.

We have made numerous attempts with goats, rabbits, and guinea-pigs to produce an antibody to this poison, but have met with only negative results, and I have concluded that there is no antibody to this poison. Certainly there can be obtained from the animals with which we have worked nothing comparable to the antitoxin of diphtheria.

We have attempted to immunize animals against the living typhoid bacillus by repeated treatments with non-fatal doses of the free poison, and to a very mild degree we have succeeded in this. By proceeding carefully and gradually increasing the doses a point may be reached where the animal bears from two to three times the amount that would surely kill an untreated animal. Animals brought into this condition, whether it be one of increased tolerance or immunity, bear from two to four times the fatal quantity of the living bacillus. However, this tolerance is not specific; it can be induced quite as well with the poison obtained from egg-white, and

[3] Annales de l'Institut Pasteur, December, 1907.

it protects quite as well against the colon as it does against the typhoid bacillus, and, in my opinion, it is nothing more than increased tolerance for the poison that is common to all true proteid bodies.

I will now turn to the non-poisonous split product of the typhoid bacillus. This is the specific part of the cell; it is the antigen or the haptophor, and in it lies, in my opinion, the most promising hope for the specific treatment of typhoid fever. I have called this portion the "residue," as the part left after the extraction of the poison. The residue makes up about two-thirds of the weight of the cell substance; however, just as the poison consists largely of inert matter, so does the residue contain much that has no immunizing properties. As obtained by splitting up the cellular substance with the alcoholic solution of sodium hydroxide, the residue contains too much alkali to be injected into animals. It is, therefore, placed in Soxhlet's apparatus, extracted for some days with alcohol, then dried and powdered. To prepare a solution for use, this powder is weighed, shaken with 0.5 per cent. carbolic acid, and filtered through porcelain. Solutions thus made apparently retain their immunizing properties indefinitely. At least we have made some preparations that we have used for three years, and they are quite as efficient now as they were when freshly made. The residue, unlike the poison, is strictly specific. That from egg-white sensitizes the animal, after the proper period of incubation, to egg-white and to no other proteid, and that from the typhoid bacillus immunizes to this micro-organism and to no other. The residue does not sensitize to itself, with the exception of the residue obtained from the tubercle bacillus, which does sensitize to itself in guinea-pigs and in man. While it is not my purpose to enter into the detail of our studies of the tubercle bacillus in this paper, I will say that the tubercle proteid seems quite different from any other proteid, bacterial, animal, or vegetable, that we have studied. I have given this residue ordinarily in 10 mg. doses once a week to a patient for more than a year, with apparent benefit and certainly without any recognizable harm, and in other patients I have used a dose of 500 mg. without apparent injury, but even when the smaller dose of 10 mg. is not exceeded, if the interval between doses be six weeks or longer, the first injection after the long interval has, in two instances in the same patient, not in others, been followed by the well-marked and alarming symptoms characteristic of the so-called serum disease. I intend to give details with regard to the tubercle residue at some future time.

We have not gotten an active residue from all proteids. That obtained from casein does not sensitize to casein. This is not strange, since casein is known to differ from most other proteids in its molecular structure. It is possible that some other method of cleavage may give us a sensitizing residue from casein.

Wheeler and I[4] have proposed a theory of the action of proteid

[4] Jour. Infec. Dis., May, 1907.

residue which I will briefly summarize here, but before doing this it will be well to state as concisely as possible what we have found some of these residues to do. V. C. Vaughan, Jr.,[5] and Wheeler and I[6] have reported on the production of immunity to the colon and typhoid bacilli with their respective residues. In doing this work we have found it convenient to designate the minimum fatal dose of a twenty-four-hour beef-tea culture of the living bacillus as a unit in the measurement of the degree of immunity secured.

A single intraperitoneal injection of from 10 to 50 mg. of the typhoid residue protects a guinea-pig against at least twice the minimum fatal dose of a living culture of the typhoid bacillus given any time between the end of the first and of the fifteenth day after treatment with the residue. Frequent treatments with 10 to 50 mg. of the residue at intervals of two or three days give a more marked and a more lasting immunity against the living bacillus. With from six to nine such treatments the animal will bear from eight to ten times the minimum fatal dose of the living organism. If a small dose of the residue, not more than 12.5 mg., be given a guinea-pig intra-abdominally, and a minimum fatal dose of the living germ be injected within thirty minutes, the animal does not die, but if 50 mg. of the residue be given, and this be followed within thirty minutes by the minimum fatal dose of the living culture the animal will die, and indeed it may die from a smaller dose than that necessary to kill a control. To give the exact figures, we have found that 12.5 mg. of the typhoid residue protects a guinea-pig against six units of the living culture administered thirty minutes later, while 100 mg. of the residue so increases the susceptibility of the animal than even less than a single unit kills it.

The residue from egg-white, as has been shown by Wheeler and myself[7] and the residue from the proteids of the serum of the horse, as shown by Nicolle and Abt,[8] sensitize animals to their respective unbroken proteids. If the residue of egg-white be injected into a guinea-pig and ten days or more later this animal be treated with unbroken egg-white, it will be found that the animal is sensitized, it is made sick, and if the dose of egg-white is sufficient, it is killed. On the other hand, if the residue of the typhoid bacillus be injected into a guinea-pig, and later the animal be inoculated with six times the minimum fatal dose of a living typhoid bacillus, the animal will not die. The residue of egg-white or that of serum albumin sensitizes animals, while the residue of the typhoid or that of the colon bacillus immunizes animals. The sensitized animal dies from the second treatment, the immunized animal is protected. These conditions are apparently antipodal, and yet I hold that they are identical in essence. The residue of egg-white or serum albumin

[6] Jour. Med. Research, 1905, xiv, 67.
[7] Jour. Infec. Dis., June, 1907.
[8] Annales de l'Institut Pasteur, February, 1908.
[5] New York Med. Jour., June 22, 1907.

sensitizes the animal by developing in it a specific proteolytic ferment which is stored up in certain cells in the animal body as a zymogen; when, subsequently, unbroken egg-white or serum albumin is injected into the animal, this stored up zymogen is activated and the injected proteid is broken up so rapidly and its poisonous part is set free so abundantly that it combines with certain receptors in the cells of the respiratory centre, and kills the animal. Likewise the residue of the typhoid bacillus sensitizes the animal by developing a specific, proteolytic ferment, which is stored up in certain cells in the animal body as a zymogen; when, subsequently, the living typhoid bacilli are injected into this animal, the zymogen is activated and splits up the bacilli before they have time to multiply and produce a fatal dose of the specific poison. Egg-white does not kill the animal sensitized by its residue unless the amount given is sufficient to supply a fatal dose when it is split up. On the other hand, when the living typhoid bacillus is injected into an animal sensitized by its residue it will quickly kill it if it be injected in sufficient amount to supply a fatal dose of the poison when it is split up. In usual parlance, when we say that one loop or 1 c.c. of a given strain of the typhoid bacillus is fatal to guinea-pigs, we mean that animals inoculated with this amount die, but we do not mean that this amount kills them; it is what this amount develops into, during the ten or more hours of inoculation, that kills. Now, the difference between sensitizing an animal to egg-white with its residue and immunizing an animal to the typhoid proteid with its residue is wholly apparent and not real. In essence they are not two things, but one. The apparent difference arises from the fact that in one instance we are dealing with a dead, stable proteid, and in the other with a living, labile proteid. In both instances we are dealing with proteid susceptibility and sensitization.

When a proteid is split up in the body of an animal sensitized to it, it yields the same poison that we have obtained by cleavage of the proteid with alkali in alcohol. The animal that dies from the toxophor group split off chemically from egg-white and the one that dies from the injection of egg-white after sensitization die from the effects of the same poison just as truly as the man who dies from morphine and the one that dies from opium die from the same poison. In both the poison comes from the egg-white. The symptoms are identical in every particular; they originate in the same time, proceed in like order, and terminate alike; the mode of death is the same and the postmortem findings are identical. I must conclude that the process of sensitizing an animal to a proteid consists in developing in its body a substance or a ferment which splits up that special proteid just as the alcoholic solution of alkali does in the retort, but much more promptly and efficiently. That the proteid is split up in the animal body so as to furnish the same poison that is obtained in the retort there seems no opportunity for

reasonable doubt. Whether the sensitizing or immunizing residue results from the cleavage that occurs in the animal body is a question for the affirmation of which we have the following evidence: (1) If several guinea-pigs be killed by intraperitoneal inoculation with the typhoid bacillus, and the exudate that forms be removed and be freed from cellular elements by filtration through porcelain, this filtrate acts exactly like a solution of the residue as we have prepared it *in vitro*. Large doses of this filtrate given simultaneously with an inoculation of the living bacillus apparently increase the susceptibility of the animal, while a small dose increases the resistance of the animal to an inoculation made later, and repeated doses of the filtrate given at intervals of from two to three days give to the animal a marked immunity to the living bacillus, and this immunity is specific as is that obtained by our residue. The identity of this split product obtained by the cleavage of the bacterial cell in the animal body with the aggressin of Bail seems to me quite evident, or at least highly probable. (2) As was first shown by Gay and Southard,[9] the blood serum of an animal sensitized to the blood serum of another animal contains a sensitizing body, as may be shown by treating a fresh animal with it, and Nicolle and Abt[10] have shown that the residue obtained by splitting up the proteids of blood serum by our method sensitizes animals to the unbroken blood serum. Wheeler and Vaughan[11] have shown that the peritoneal washings from sensitized animals, dead from second injections, sensitize fresh animals.

From these findings I conclude that in the animal body the typhoid or colon proteid or egg-white, or serum albumin or serum globulin, or, in short, any true proteid is split up into residue and poison, much the same as it is in the retort by our method, but much more completely and perfectly. While the poison that kills in typhoid fever is the same in essence with that which we obtain from the typhoid proteid, the residue that sensitizes is also the same, whether it be obtained by chemical cleavage *in vitro*, or by the more perfect chemical cleavage *in vivo*. In one instance the active agent is the hydrolytic effect of dilute alkali; in the other it is a specific, proteolytic enzyme.

I will now attempt to apply this knowledge that we have obtained in the study of the chemistry of the typhoid bacillus, and the method of securing immunity to it to the disease of which it is the cause. In making this attempt I wish to state that what I may say is tentative and subject to modification from a wider and more exact knowledge that may come from more extended research. I do not say that an antibody to the typhoid poison will never be secured, but I do say that such a discovery is not probable. The fact that the fatal

[9] Jour. Med. Research, 1907, ii, 143.
[10] Annales de l'Institut Pasteur, February, 1908.
[11] Jour. Infect Dis., June, 1907.

effect of the poison may be prevented by ether anesthesia is encouraging, and it is within the range of possibility that some more practical and usable agent to accomplish the same purpose may be secured.

When one becomes infected with the typhoid bacillus there is a period of incubation which, according to our best information, lasts some ten days or longer. In the guinea-pig inoculated with a fatal dose of the typhoid bacillus, the period of incubation continues for ten or more hours. During this period in both the man and the animal the bacillus multiplies, and yet there is no evidence that either the man or the guinea-pig is for the time being aware of the abnormal condition, or conscious of the presence of the undesirable guest. The sickness begins when the animal body becomes sensitized and begins to split up the bacilli. It is probable that this sensitization does not occur until some of the bacilli undergoing autolysis or being broken up by phagocytic action furnish the soluble residue which can reach a large portion of the body cells. We know that an individual may carry the typhoid bacillus in his gall-bladder or urinary bladder or in an abscess for years without having typhoid fever. The bacillus grows and multiplies in one of these cavities, and in greater or less numbers breaks up. The poisonous portion, being diffusible, is taken into the circulation and causes more or less marked departure from health, but the residue being non-diffusible, there is no general sensitization of the body.

Proteid sensitization may be local or general. There are certain reasons for believing that the sensitizer must reach a body cell before it can sensitize it. This is the reason why the residue fails to sensitize so long as it is confined to a cavity, such as the gall-bladder, and it also explains why the soluble residue produces general sensitization while the unbroken bacillus acts only locally and imperfectly. Moreover, this explains the development of acute poisoning with such soluble proteids as egg-white, blood serum, milk, etc. It is impossible to induce such explosive reaction with non-soluble proteids such as living or dead bacilli. When the first or sensitizing dose of a soluble proteid is administered every cell in the blood and lining of the bloodvessels is reached, and again, when the second or poisonous dose is administered the same cells are reached practically at the same moment, and according to our theory the zymogen in all these cells is activated at the same time, and the effect is explosive—an effect that can be produced only by soluble bodies. Again, when the poison is set free slowly much of it is probably fixed by the immediately surorunding tissue and the disastrous effect on the life of the animal that comes from an overwhelming action on the respiratory centre is avoided.

The fact that the administration of a large dose of the residue simultaneously with or very near in point of time with the inoculation with the bacillus increases the susceptibility of the animal,

while a much smaller dose of the residue increases the resistance, and repeated doses give immunity is an interesting fact. I have interpreted this finding as follows: The residue converts the zymogen into an active ferment, and, at the same time absorbs it. The attraction is between the residue and the ferment. The latter combines with the former more readily when it is free than it does when the residue is still a part of the bacterial cell. When large quantities of the residue are given the activated ferment is all or largely taken up by the free residue, and there is no splitting up of the bacterial proteid; consequently, the bacillus multiplies without hindrance; but when the zymogen is activated by only a small amount of residue, the greater part of the ferment is used in splitting up the bacilli. This is, I think, an important point, and in using the residue in the treatment of typhoid fever must always be borne in mind, because it must determine the dose of residue to be administered.

If the residue acts upon man as it does upon guinea-pigs, it should prove an efficient, but a temporary, vaccine against typhoid fever. In guinea-pigs a single injection of the residue gives the animal protection against twice the fatal dose of the living bacillus for about forty days, and it is presumable that it would protect against natural infection in which the number of bacilli introduced is much smaller for a longer time. That Wright's vaccination against typhoid fever was of some service in the Boer campaign seems quite well substantiated, but he employed the unbroken bacillus, while in animals at least the residue is much more efficient, because, as I have attempted to explain, the soluble residue gives a more general and consequently a more efficient sensitization than the unbroken bacillus, since the latter has to be split up before it can give any general sensitization at all. Besides, the residue causes no local irritation or inflammation about the point of injection, and the sensitization produced by it is systemic from the start. However, the possible use of the residue as a vaccine is not the special purpose of this paper, and the subject will not be farther pursued at present.

If my interpretation of our experimental work be correct, whether one treats typhoid fever with the residue obtained by splitting up the bacillus chemically or with the blood serum of an animal that has been treated repeatedly with the unbroken typhoid bacillus, in either case he uses the residue. In one case the residue has been obtained by chemical cleavage of the typhoid proteid *in vitro*, and in the other the residue has been obtained by ferment cleavage *in vivo*. An animal may be sensitized to egg-white by the residue obtained chemically as shown by Wheeler and I, or with the blood serum of a sensitized animal, as shown by Gay and Southard; or, an animal may be immunized with the residue of the typhoid bacillus obtained chemically, or by the filtered peritoneal exudate of an animal killed with the living typhoid bacillus. It is the residue in either instance that sensitizes or immunizes. If this be true there is every advantage

in favor of the employment of the residue obtained chemically. First, it is much less expensive to obtain the residue by chemical cleavage than by administration of the bacillus to animals; second, the residue makes a much better preparation, it is less bulky, and does not contain all the foreign matter that is contained in blood serum; third, in employing blood serum one risks sensitizing his patient to the proteids of blood serum while the residue does not sensitize to itself; and fourth, the dosage may be determined accurately with the residue obtained chemically.

If typhoid fever could be recognized in its early stages when sensitization and cleavage of the bacillus is only local and imperfect, then I should hope for great advantage in its treatment with the residue. This soluble sensitizing agent acting promptly as it does, might be expected to split up the bacilli before they become so numerous, and the abortion of the disease might be easily brought about. Reed, Shakespeare, and I[12] ascertained that many of the light febrile attacks among the soldiers in our camps in 1898 were typhoidal; they gave at least temporary immunity to the disease, and they responded to the Widal test. These abortive attacks are best explained on the ground of early systemic sensitization and destruction of the bacillus. Furthermore, we found that in its early stages typhoid fever is often apparently intermittent, and this is best explained as due to local and incomplete sensitization. If the disease could be generally recognized in this stage the residue should be of great service in aborting the disease. In this stage small doses of the residue, not more than 50 mg. should prove of marked service. It is to be hoped that some means for the early and positive diagnosis of this disease will soon be discovered.

The problem is quite a different one when it comes to the treatment of well developed typhoid fever, when there is an abundant bacteremia. In this stage one of the dangers to life is the too rapid and abrupt cleavage of the bacilli with the liberation of the poisonous group in such quantity that it may overwhelm the nervous system. Even here, however, the residue may be of service in the saving of life if wisely used, but it may prove a two-edged sword and cut both ways if not used with intelligence. Larger doses of the residue by absorbing or combining with the specific proteolytic ferment may retard the cleavage of the bacillus, diminish the quantity of poison set free in a certain time, and save the life of the patient, but with the effect of prolonging the disease as Richardson[13] has shown.

Richardson has shown the apparent value of the residue in preventing relapses in typhoid fever. The employment of the residue for this purpose seems to me rational and in accord with the general statements that I have made. In this disease there are often espe-

[12] Report on the Origin and Spread of Typhoid Fever in U. S. Military Camps during the Spanish War of 1898.

[13] Boston Med. and Surg. Jour., 1907.

cially resistant bacteria that escape the general lytic cleavage that destroys most of their fellows. These withdraw into the tissues, multiply, and then venture again into the circulation. Richardson's work apparently shows that a judicious stimulation of the function of sensitization serves a valuable purpose in preventing these relapses.

In conclusion I wish to say that, so far as I can see today, it is not probable that we will ever get an antitoxin for the treatment of typhoid fever comparable with that which we have for diphtheria, but that the residue may be of service, especially in preventing relapses, and if we can find some method of early diagnosis it may prove of value in aborting the disease.

OBSERVATIONS ON THE HYPODERMIC USE OF QUININE AND UREA HYDROCHLORIDE IN THE DIAGNOSIS AND TREATMENT OF ACUTE AND CHRONIC MALARIAL INFECTIONS,

AND ON THE RESEMBLANCE TO THE SEXUAL CYCLE OF THE HEMAMŒBA MANIFESTED BY THE PERIODS OF FREEDOM FROM PAROXYSMS THAT ORDINARILY FOLLOW A SINGLE INJECTION OF ABOUT ONE GRAM OF THIS SALT.[1]

By Solomon Solis Cohen, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA; PHYSICIAN TO THE JEFFERSON MEDICAL COLLEGE HOSPITAL AND THE PHILADELPHIA GENERAL HOSPITAL.

The object of this paper is to recall attention to four points in connection with the hypodermic use of quinine and urea hydrochloride in acute and chronic malarial infections: (1) The superiority of this salt over other preparations of quinine. (2) The periods of either six and one-half days approximately, or thirteen days approximately, during which patients previously exhibiting irregular recurrences of paroxysms, or regular quotidian, tertian, or quartan recurrences, remain free from paroxysms following a single injection of about 1 gram (15 grains) of this salt. (3) The similarity between these periods of six and one-half and thirteen days respectively, and the periods of cyst formation and of sporozoite development in the sexual cycle of the parasite, as observed in the mosquito. (4) The diagnostic value of such injections, both in proving and in disproving malarial infection in cases in which parasites have not been discovered in the peripheral blood.

[1] Read by title at the fifth annual meeting of the American Society of Tropical Medicine, Baltimore, March 28, 1908.

A fifth point may be emphasized in passing, as a variant of the first, namely, the probable therapeutic superiority of this quinine salt in pernicious malaria.

In connection with the similarity between the significant periods of the sporogony of the hemamœba and the week and two-weeks freedom periods following the use of quinine in this active form, I have sought, and had search made, for gametes and sporozoites, but without success. I am extremely desirous that the observations should be repeated by observers more skilled in technique and in parasitology, than I and having more continuous control of abundant material.

My experience with the use of the double hydrochloride of quinine and urea in the treatment of malarial infections dates from 1884, when I was chief of clinic in the Medical Out-patient Department of the Jefferson Medical College Hospital, in the service of Professor Roberts Bartholow, whose praise of this preparation led me to its use. Its advantage is extreme solubility, as it dissolves in its own weight of water, thus making possible the administration of a sufficient dose, which is quickly absorbed. Its disadvantage is the liability to produce slough or abscess if one is not careful in the use of the preparation. With due care to make the injection deeply under the skin, but not necessarily into the muscle, and to empty the syringe before withdrawing the needle, so that no drop of the solution shall fall upon the integument as the needle leaves the tissues, such accident need not be feared. An additional precaution invariably employed in my service is to seal the point of puncture with iodoform collodion or with tincture of iodine.

In G. E. de Schweinitz's experiments[2] upon quinine amblyopia, he found the quinine and urea salt much more toxic than any of the other preparations which he employed. Incidentally to the therapeutic studies summarized in the following pages, observations have from time to time been made as to the effect of the drug upon leukocytosis. So far as the gross leukocyte count is concerned, it frequently seemed to reduce the number slightly, but this effect was not invariable, nor did the decrease persist for more than forty-eight hours after the injection. Not rarely, the fall would be followed by an increase above the previous figure. As to differential counts, the observations are insufficient and inconclusive.

Acute Malarial Infection.—The observations which here are summarized have been carried out in private practice, at the Jefferson Medical College Hospital, both in the Out-patient Dispensary and in the wards, and at the Philadelphia Hospital. Unfortunately, some of the records have been mislaid, so that accurate statistics cannot be given. Approximately, there have been treated by this

[2] Personal communication; also G. E. de Schweinitz, Toxic Amblyopias, Philadelphia, 1896, p. 193

method about 250 cases of acute malarial infection, of which 1 was of quartan periodicity, upward of 100 of quotidian periodicity, and upward of 140 of tertian periodicity, the remaining 5 or 6 exhibiting irregular recurrence. In the 1 case recorded as of quartan periodicity the parasite was identified as the quartan parasite (Hæmamœba malariæ). In the others the tertian parasite, of the ordinary (Hæmamœba vivax) or estivo-autumnal (Hæmamœba falciparum) type was, in general, recognized. Unfortunately, the records, while noting the presence or absence of organisms, fail to specify in a sufficient number of cases the exact variety found. It is possible that in some cases quotidian parasites were present and not identified.

In all cases of which note was made, with the exception of 4 instances in which two injections were necessary to bring about the freedom period, there occurred, following a single injection of 1 gram of the quinine and urea salt, especially if this were administered during the paroxysm or within four hours thereafter, a prolonged, definite period of freedom from paroxysms. In about one-third of the cases this lasted between six and seven days, varying from one hundred and forty-one to one hundred and sixty-two hours; in the remaining two-thirds of the cases, the period of freedom was between twelve and fourteen days, varying from two hundred and ninety to three hundred and twenty-five hours. In some of the case-notes these periods are estimated from the beginning of chill to the beginning of chill, and in some cases from the hour of maximum temperature to the hour of maximum temperature. In future observations a uniform method should be followed. It is also quite possible that nurses on duty do not always catch the exact beginning of a chill, or the exact point of maximum temperature. I am inclined to believe that a fair statement of the average freedom periods would be six and one-half and thirteen days respectively; or perhaps it might be stated as seven and fourteen (week and fortnight) *organism days* of about twenty-one to twenty-two hours each. The most frequent figures to be found in the notes concerning the week-cycle are one hundred and forty-seven, one hundred and fifty, and one hundred and fifty-six hours; in the notes concerning the fortnight cycle, three hundred, three hundred and six, and three hundred and twelve hours. As a rule, but not invariably, the cases showing the shorter period of freedom were quotidian in type. Of those exhibiting the larger period, the preponderating number were tertian. The quartan case showed a freedom period of twelve and three-eighths days, with certain peculiarities, a summary of which is given later.

When the injection is made within less than two hours before the time of an expected paroxysm, it usually does not prevent the occurrence of the chill, although the phenomena are, in general, milder than usual. The paroxysm due to follow will, however,

be missed, and the freedom period thereafter be manifested. When the injection is given three or four hours before the time at which a paroxysm is anticipated, it usually prevents the attack. When given between four and eight hours in advance of the expected chill time, the injection will usually prevent both the paroxysm about to be due and its anticipated successor, but sometimes only the latter. The effect cannot be predicted with certainty.

Usually the paroxysms, if tertian, would, after the thirteenth day, resume their former periodicity; or, if quotidian, would, after six and one-half or thirteen days, change to tertian. Rarely did the paroxysms resume the quotidian periodicity. A case of irregular periodicity would assume the tertian, less frequently the quotidian, type. In one instance there is a note made that the paroxysms changed from quotidian to quartan, but as the detailed records are missing and the case dates back to 1885, at which time the specific quartan parasite would not have been recognized, no stress is laid upon this fact.

In other cases, of which 6 are noted (probably all that were observed), after the six and one-half days or thirteen days of freedom, a further freedom period of six and one-half or thirteen days was manifested without further medication; that is to say, the periodicity apparently changed from quotidian or tertian, as the case might be, to what were formerly termed, respectively, the weekly and the fortnightly types. The number of possible observations of this kind was limited, for obvious reasons.

After the occurrence of the freedom period had been demonstrated, and the periodicity of the renewed paroxysms determined, injections were, as a rule, resumed and continued daily in quotidian cases, and on alternate days in tertian cases, until the recovery of the patient was assured; or the drug was administered by the mouth —in capsule—in two doses of 10 or 12 grains (0.75 gram) each, four hours and eight hours, respectively, before the anticipated chill time; or 10 grains (0.65 gram) were given at night and the same quantity in the morning, without special reference to the chill period; or one dose of 20 to 23 grains (1.3 to 1.5 grams) was given between eight hours and four hours before the anticipated chill. On the whole, one method answered as well as another.

When two weeks had passed without paroxysms, the patient was usually dismissed from the hospital, with the injunction to take 20 grains of the drug weekly, in two doses, one of 10 grains on the evening of the sixth day, and one of 10 grains on the morning of the seventh day, calculating from the date of the last paroxysm; and to continue this treatment for at least three months, returning to the hospital or reporting to the Out-patient Department from time to time, for observation.

The case of H. J., observed in October and November of 1907, may be related as a typical instance, illustrating several of the phenomena summarily described (Chart I).

This man had a quotidian intermittent fever, with paroxysms recurring in alternate periods of twenty-one and twenty-four hours. He exhibited the ordinary tertian parasite, and was evidently infected with two broods, maturing at forty-five hours. An injection was given fifty minutes before a paroxysm expected at 11 A.M., on October 26. The chill occurred on time, but its duration was much shortened. The temperature, which in previous attacks had risen to 104° or 105° F., reached only 103°, and fell to the minimum point, 97°, five hours after its maximum had been reached, the fall in previous paroxysms having occupied eight hours. There was no chill on the following day, and the temperature remained practically normal, oscillating between 97° and 98.4° until one hundred and forty-seven hours after the chill, or one hundred and forty-two hours after the temperature had fallen to its minimum. On November 1, the sixth day after the last preceding paroxysm, or the seventh day, including the day of that paroxysm, the temperature rose at 2 P.M. to 102°, remaining elevated for three hours, and reaching normal at 8 P.M., but there was no chill; the paroxysm was incomplete. On November 3, at 9.45 A.M., about forty-three and one-half hours after this incomplete paroxysm, a chill began, and the maximum temperature point of this attack, 104°, was reached at 11 A.M.; that is, about forty-five hours after the maximum point of the paroxysm without chill that had preceded it. The temperature reached its minimum at 8 P.M. A chill occurred at 7.15 A.M. on the fifth of November, again about forty-five and one-half hours after the previous chill, maximum temperature being reached at 8.45 A.M., and minimum temperature not until 2 A.M. the following day. The next chill occurred on the 7th of November at 7.45 A.M., forty-eight and one-half hours after the previous one, maximum temperature occurring at 11 A.M. and minimum temperature at 11 P.M. The fall of temperature was possibly hastened by the second injection of quinine and urea hydrochloride, which was given during the declining stage of this paroxysm, at 2 P.M. No further paroxysm was permitted to occur. The treatment was continued by injections on alternate days until November 16, and the patient left the hospital, apparently well, on November 18.

Examination of the blood had shown the presence of parasites in various stages; hyaline, pre-segmenting, segmenting, intracellular pigmented, and extracellular pigmented forms being present, all in large numbers.

October 24. 200 fields were counted and 600 parasites found.

October 25. A similar count was made.

October 26. 200 fields were counted; 560 parasites were found. On this day an injection was given.

October 27. 200 fields were examined; 12 parasites were found—8 intracellular pigmented and 4 extracellular.

October 29. 200 fields were examined; 3 parasites were found—2 intracellular pigmented and 1 extracellular.

October 30. 500 fields were examined; no organisms were found.

October 31. 500 fields were examined; no organisms were found.

November 1 (the sixth day after the injection). 200 fields were examined; 34 parasites were found—young hyaline, 31; mature intracellular, 2; extracellular pigmented, 1. It was on this date that the temperature reached 102° at 2 P.M.

November 2. 200 fields were examined; 90 parasites were found—hyalin, 8; intracellular pigmented, 60; pre-segmenting, 22; segmenting parasites were specially looked for, but none found.

November 3. 200 fields were examined; 49 parasites were found—hyaline, 22; intracellular pigmented, 10; pre-segmenting, 16; segmenting, 1. On this day the chill occurred, with a temperature of 104°.

November 4. 200 fields were examined; 288 parasites were found—hyaline, 20; intracellular pigmented, 264; segmenting, 4. Temperature was 102° at the time of observation, but no chill occurred.

November 5 (last chill day). 200 fields were examined; 236 parasites were found—hyaline, 188; intracellular pigmented, 32; segmenting, 16. Injection was given on this day. No further chill occurred, and the number of parasites steadily diminished until finally they disappeared.

The accompanying charts, for which I am indebted to Drs. Robinson and Moore, internes at the Philadelphia Hospital, exhibit the decrease, disappearance, and return of parasites in this case and the temperature curves indicative of periodicity and freedom preceding and following the injection of the drug (Charts I, II, III).

One other case—that of quartan fever, being the only example of its kind in the series—may be cited in brief summary. It shows a period of freedom of twelve days and nine hours, interrupted by abortive disturbances on the intermediate days of paroxysm, and an apparent tendency to alternate periodicities of seventy-eight and eighty-four hours respectively. Whether the twenty-one-hour and forty-two-hour disturbances noted may not have some relation with quotidian and tertian periodicities, and what are the possibilities of a multiple infection, or of changes of type in organisms, are questions suggested by the case, but not answered (Chart IV).

Cosmo di G., aged twenty-three years, a native of Italy, by occupation a laborer, came into the hospital on June 17, 1907, with a history of having had an attack of chills and fever in Italy four years earlier, the paroxysms, according to the patient's statement, recurring after intervals slightly in excess of three days. The duration of this attack was three weeks, and the patient, although he suffered from irregular fever on various occasions thereafter, had had no second attack. The present illness began about five weeks before admission to the hospital, with a violent chill, which lasted about three hours and was followed by fever and sweating. Later, severe muscular pains developed, with extreme tenderness, especially of the trunk and abdomen. This was followed by the appearance of

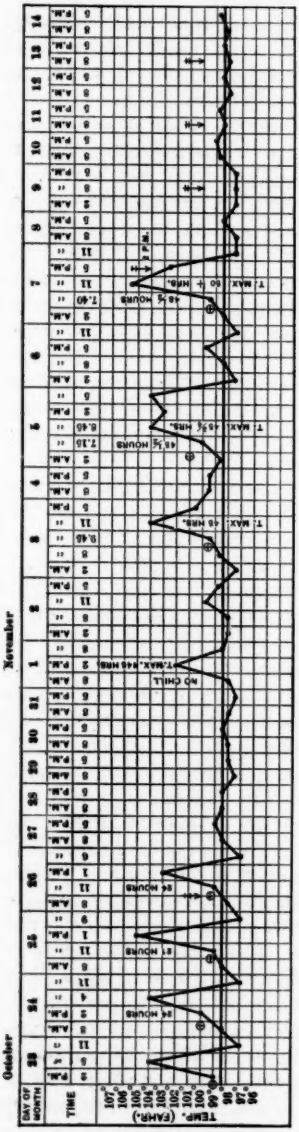


CHART I.—Quotidian intermittent fever. Free period 147 hours. Change of type to tertian. (Henry J.; Autumn, 1907.)

* Beginning of chill. ‡ Injection of 1 gram of quinine and urea hydrochloride.

what, from the patient's description, seems to have been a maculo-papular eruption, lasting about one day. According to the patient's statement, these paroxysms recurred every third day, and were followed by a like eruption. He had been given some pills, presumably quinine sulphate, but had not recovered.

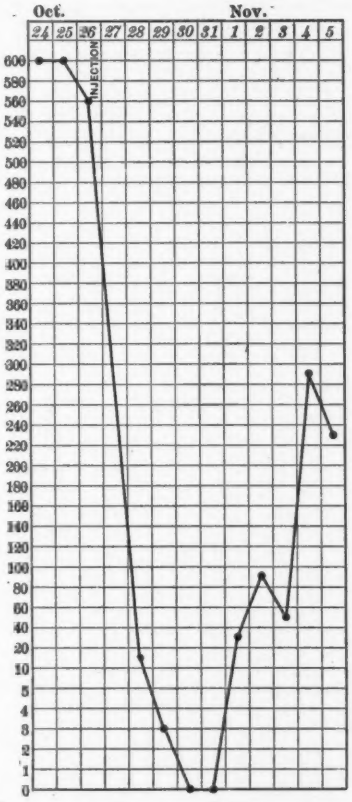


CHART II.—Showing disappearance and reappearance of organisms after the injection of 1 gram of quinine and urea hydrochloride. (Case of H. J.)

Physical examination of the patient upon admission revealed nothing significant, other than slight enlargement and tenderness of the spleen. Irregularly distributed over the trunk and abdomen was a papulo-œdematous eruption, consisting of central spots of a pinkish color, surrounded by a purplish areola. This gradually faded, reappearing with high temperature paroxysms. After treat-

ment was begun it disappeared altogether. The temperature upon admission was 101.3° at 5 P.M., June 17. Chart IV shows the course of the temperature during the patient's stay in the ward. Previous to the injection of 1 gram of quinine and urea hydrochloride, three periods of maximum temperature (about 103° F.) were noted, the intervals being, respectively, eighty-four hours and seventy-eight hours. Periods of minimum temperature (about 97° F.) followed the maximum temperature after intervals of, respectively, twenty-four, thirty-six, and twenty-four hours. Each of the periods

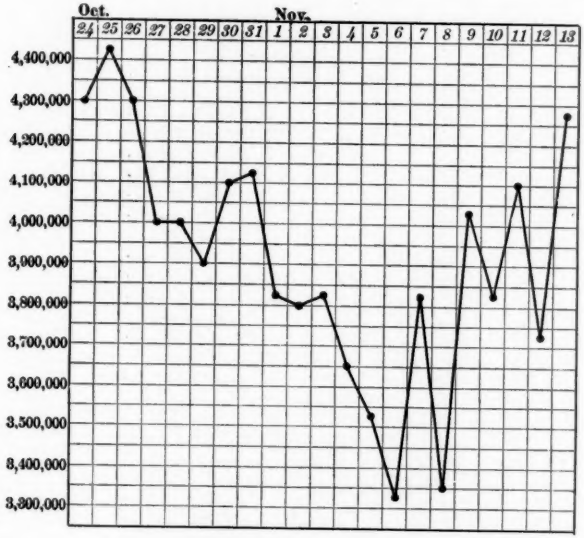


CHART III.—Erythrocyte count diminished after injection of quinine and urea hydrochloride (October 26), until disappearance of recrudescent organisms; then increasing interruptedly. The leukocytes varied during this period from 4600 to 4000, falling to the latter number on October 28, when the temperature became normal following the injection, and the parasites were only 12; they gradually rose, with remissions in count up to 4400 on November 5, when the temperature was 104.2°, and the number of parasites was 236. (Case of H. J.)

of maximum temperature was preceded by a chilly sensation and followed by sweating. The decline of temperature to the normal point, or just above, occurred in from three to twelve hours, without medication.

The blood on the day following admission showed: hemoglobin, 100 per cent.; erythrocytes, 5,104,000; leukocytes, 13,800—polymorphoneuclear, 73 per cent.; small lymphocytes, 13 per cent.; large lymphocytes, 13 per cent.; eosinophiles, 1 per cent. No organisms were found in several slides prepared from the fresh blood, nor were

they discovered either in stained or unstained specimens until the 26th, when intracorpuscular forms were seen. On the 28th, the day on which the paroxysm, if quartan, was again due, both intra-

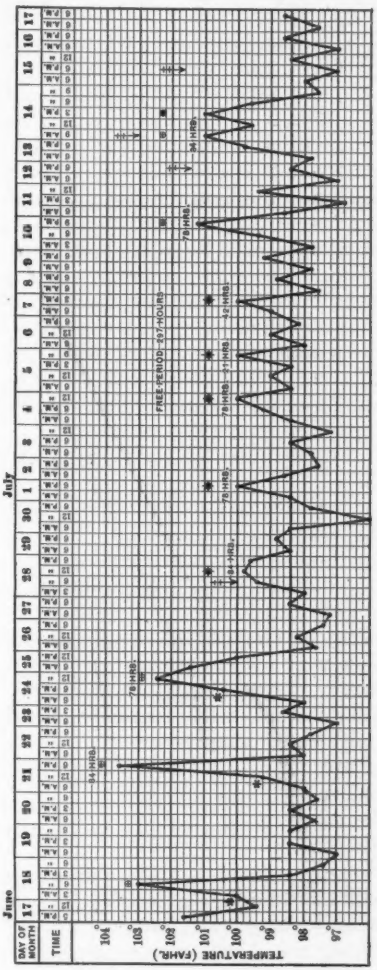


CHART IV.—Quartan intermittent fever. Free period 297 hours. (Cosmo di G.; Summer, 1907.)
* Beginning of chill. • End of chill.
✦ T. rise without chill. ▪ Double crest temperature rise.
‡ Injection of 1 gram of quinine and urea hydrochloride.

corpuscular and extracorpuscular forms were identified as the quartan parasite.

On June 28, at 6 A.M., six hours in advance of the paroxysm anticipated on that day, which was apparently due to occur eighty-four

hours after the preceding paroxysm, the injection was given, the temperature at that time being 99.4°. No chilliness was felt, but the temperature rose 4 points to 99.8° F., about 3° less than the preceding maximum point and 4° less than the paroxysm with which its period of eighty-four hours apparently related it. No further injection being given, a period of temperature rise (100°) manifested seventy-eight hours later, another rise, again after seventy-eight hours, another twenty-one hours later, and another forty-two hours later. The patient complained of nothing. There was neither chilly sensation nor what might be considered marked rise of temperature until July 10, at 9 P.M., seventy-eight hours after the rise of temperature last noted, two hundred and ninety-seven hours (twelve days and nine hours) after the abortive temperature rise following the injection, and three hundred and eighty-one hours after the last preceding definite paroxysm. The next paroxysm, with a temperature rise to 101°, occurred July 14, at 9 A.M., the interval being eighty-four hours. This paroxysm shows a double crest, the second rise occurring six hours later than the first. Following this, injections were given at such intervals as to control the paroxysms and assure recovery from the acute attack. Treatment appropriate to chronic malarial infection was then instituted.

During the period of observation the following notes were made concerning organisms:

June 26. Malarial organisms found—intracorpuscular forms.
June 27. Malarial organisms found.
June 28. Organisms—quartan—found. Injection given.
June 29. Coarsely granular bodies—intracellular, peripherally located. A few hyaline bodies found.
June 30. Extracorpuscular and intracorpuscular bodies found. The intracellular bodies were oval in shape.
July 1. None found.
July 2. Intracellular bodies, with coarse pigment, sluggishly motile; extracellular pigmented bodies.
July 3. Same as above, pigment more peripheral.
July 4. Same as above.
July 5. Nothing found.
July 6. Nothing found.
July 7. Nothing found.
July 8. Motile bodies (intracellular) found.
July 9. Motile bodies (intracellular) found
July 10. Temperature rise. Intracorpuscular forms and extracellular motile bodies found.
July 11. Intracorpuscular forms and extracellular motile bodies found.
July 12. No parasites found.
July 13. Parasites found, pre-segmenting forms.
July 14. Paroxysm. Injection given. A few parasites.

July 15. None found.
July 18. None found.
July 30. None found.

Temperature charts are also shown of a number of cases taken at random (Charts V, VI, VII). It will be observed that in one of these quinine chlorhydrosulphate was used instead of the urea salt and was in this instance efficacious. Other observations were made with it. While therapeutically active, it did not prove so uniformly dependable as the urea salt in the matter of the defi-

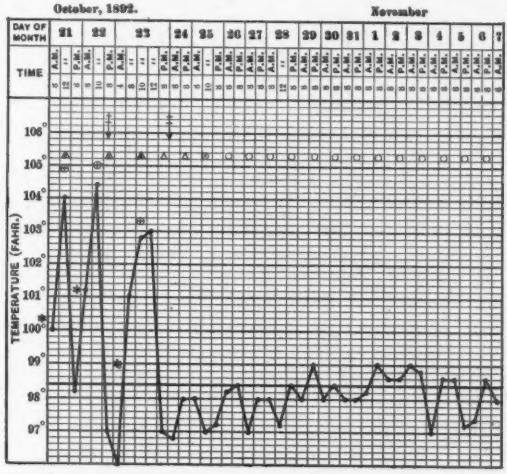


CHART V.—Quotidian intermittent of 30 days' duration prior to treatment. Two injections. Recovery. (John S.; Autumn, 1892.)

* Beginning of chill. ⊕ End of chill.

† Injection of 1 gram quinine and urea hydrochloride.

▲ Organisms, pigmented, numerous.

△ Organisms, pigmented, few.

⊕ Organisms, hyaline, few

○ No organisms.

nite freedom period. Drawings of parasites observed were made in 1892, by Dr. Claribel Cone, then interne at the Philadelphia Hospital and now professor of pathology in the Woman's Medical College of Baltimore, to whom I am also indebted for careful notes of the cases which were under her immediate care.

CHRONIC MALARIAL INFECTIONS.—In chronic malarial infections of long standing, especially in those cases which exhibit considerable enlargement of the spleen or liver, or both, with or without marked alterations of the blood, quinine alone, even in the form of the combination with urea, has not been sufficient to bring about recovery.

The quinine and urea salt, however, has seemed more efficacious than other preparations of cinchona and its alkaloids, with the exception of cinchonidine salicylate, and in no case has treatment without quinine been so satisfactory as when quinine has been used in con-

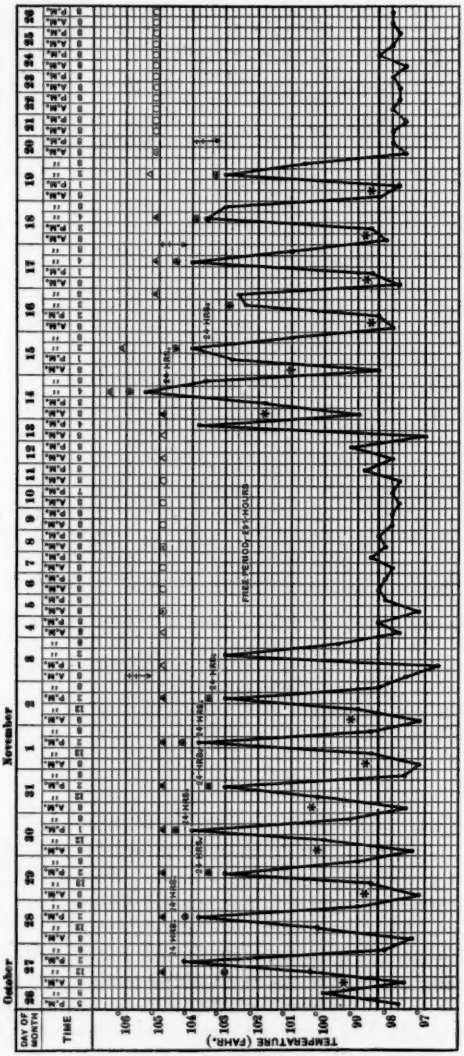


CHART VI.—Quotidian intermittent. Free period 201 hours. (Jos. D.; Autumn, 1892.)

* Beginning of chill.
‡ Injection of quinine and urea hydrochloride.
△ Organisms, pigmented, few.
⊕ End of chill.
▲ Organisms, pigmented, numerous.
○ No organisms
⊙ Organisms, hyaline, few.

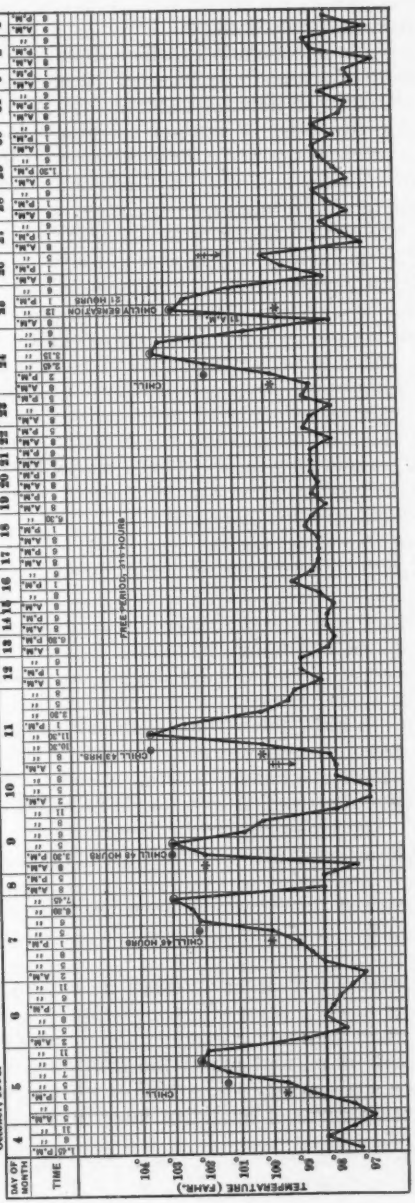


CHART VII.—Tertian intermittent. Free period 316 hours. (A. B. C.: Autumn, 1896.)

* Beginning of chill. ⊕ End of chill.

‡ Injection of 1 gram of quinine chlorhydrosulphate.

junction, at various times, with salicin, methylthionin hydrochloride, arsenic, iodine, iron, and radiotherapy.

In those cases of chronic malaria in which there is a tendency to recurrence of acute exacerbations, whether manifesting as chills and fever or as gastric or nervous disturbances, the quinine and urea hydrochloride has been of distinct advantage in two ways: (1) When the recurrence is periodic, or assumes, after its initiation, a periodic type, quinine and urea hydrochloride used hypodermically or by the mouth, in appropriate dosage, and at a suitable time, will cause the acute symptoms to disappear promptly. For the remedy of the underlying cachexia or chronic affection, other means are additionally necessary.[3] (2) In cases in which the symptoms are irregular the injection of a small dose of quinine and urea hydrochloride will frequently bring about some definite order, either in the quality or time of the symptoms; after which they can be dealt with in the same manner as cases spontaneously definite and periodic. In addition, the diagnosis is frequently made clear by the appearance in the peripheral blood of hemamœbæ, sometimes of atypical character, but still recognizable as varieties of the malarial parasite. This phenomenon will be spoken of more particularly in the next division of the subject, which concerns diagnosis.

DIAGNOSIS.—In two ways has the hypodermic use of the double hydrochloride of quinine and urea proved useful in diagnosis.

1. There are certain cases, evidently of acute infection, which resemble malarial fevers in the character or periodicity of the paroxysms, but in which malarial organisms cannot be found in the blood. There are certain other cases in which, despite the aberrant nature of the paroxysms, there is reason to suspect a malarial origin or complication, and in which, nevertheless, malarial hemamœbae have not been discovered. In nearly every instance of either of these groups the presence or absence of malarial infection can be predicated upon the patient's reaction to a single injection of the urea and quinine salt. The prolonged freedom period having been found to occur invariably in every case in which the organisms had been demonstrated, it is reasonable to assume that its occurrence indicates the dependence of the symptoms upon undiscovered, perhaps deep-dwelling parasites, and that its absence means the absence of malarial infection.

Thus, in the course of the earlier observations at the Philadelphia Hospital, at a time when 5 cases of intermittent fever of definitely proved malarial origin were under treatment, and manifesting, some the six and one-half days, and others the thirteen days, freedom period, there was a sixth patient who exhibited what appeared to be a typical temperature curve of quotidian intermittent fever, but in

[3] See also the author's articles in "The Polyclinic," Philadelphia, February 15, 1884, and January 15, 1886; and "The Philadelphia Polyclinic," March 15, 1893, and September 3, 1898.

whose blood malarial organisms could not be demonstrated. He received a diagnostic injection of 15 grains of quinine and urea hydrochloride, which induced merely a temporary fall of temperature. Renewed questioning then elicited from the patient what had theretofore been denied, namely, a history of syphilitic infection some six months previously; and recovery promptly followed the use of mercurial inunctions.

In cases of typhoid fever, in which the temperature has tended to assume, at some period of the case, an intermittent type, but in which malarial organisms have not been found in the peripheral blood, diagnostic injections have, in some instances, been followed by the freedom period and in others have not so been followed. In these

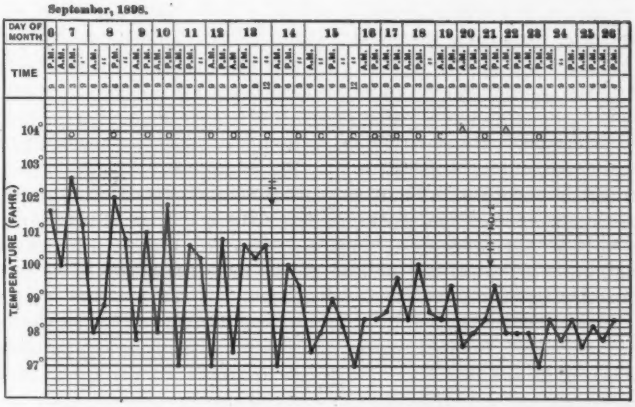


CHART VIII. (Illustrating diagnosis).—Mixed infection; typhoid and malaria. Widal reaction positive. Rose spots. (X. Y. Z.; from Tampa, Fla.)

‡ Quinine and urea hydrochloride injected. ○ No organisms found.

△ Organisms found.

instances, and especially among soldiers of the Cuban war, observed in the months of July, August, and September, 1898 (Chart VIII), it was found that the freedom period usually occurred in patients whose marked loss of hemoglobin would in any event have raised suspicion as to malarial complication, that is to say, of double infection—malaria and typhoid. In some of those in whom the quinine treatment was not continued, because it did not seem to be clinically necessary, the malarial organisms made their appearance during convalescence, after the typhoid infection had run its course. In others, the continuance of the quinine treatment presumably prevented such definite demonstration of the diagnosis. In those cases in which a single injection of the quinine and urea salt had a temporary antipyretic effect, but was not followed by a prolonged freedom

period, malarial organisms did not make their appearance so long as the patients remained under observation; and it is fair to conclude that in these cases that form of infection was absent.

2. The other method in which the injection of the quinine and urea salt has proved useful diagnostically has already been referred to in speaking of the treatment of chronic malarial infection. It was suggested to me by an old observation of Archibald Billings.[4] In cases of doubtful diagnosis the injection of a quantity of the drug not sufficient to secure a definite freedom period will frequently cause the appearance in the peripheral blood of organisms recognizable as normal or atypical forms of the hemamœba of malaria, and this has been observed so frequently and in so many diverse conditions that I am inclined to look upon its absence after, say, half a dozen injections, varying from three days to a week apart, and in doses increasing from 0.3 to 1 gram, as virtually excluding malarial infection. A typical instance of the value of this use of the quinine and urea salt is the case of chronic malarial infection with splenomegaly and blood changes resembling those of Banti's disease,[5] studied in conjunction with Dr. R. C. Rosenberger and presented to the College of Physicians of Philadelphia, in March, 1904. I am of the opinion that in such cases the organism is resting in some larval form—if the expression be appropriate—probably in the spleen or bone marrow, and that its appearance peripherally is part of a defensive, reproductive reaction to the paratoxic effect of quinine. That organisms do remain latent for long periods is well known; and I have elsewhere referred to a case in which they had reappeared annually for twenty years, provoking, usually, a gastric crisis. This phase of the subject, also, I hope some competent investigator will look into.

[4] A. Billings, First Principles of Medicine, London, 1838, p. 218.

[5] Amer. Jour. Med. Sci., August, 1904; Trans. Coll. Phys. Phila., 1904; Phila. Hosp. Reports, 1905.

THE RESISTANCE OF DIABETICS TO BACTERIAL INFECTION.

A STUDY OF THE OPSONOPHAGOCYTIC PROPERTIES OF THE BLOOD IN 74 CASES OF DIABETES MELLITUS AND RELATED CONDITIONS.[1]

By John C. Da Costa, Jr., M.D.,
ASSOCIATE IN CLINICAL MEDICINE IN THE JEFFERSON MEDICAL COLLEGE,
AND
E. J. G. Beardsley, M.D.,
ASSISTANT DEMONSTRATOR OF CLINICAL MEDICINE IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

(From the Laboratory of Clinical Medicine and Therapeutics of the Jefferson Medical College Hospital, Philadelphia.)

Diabetes mellitus, always an inviting field for research, appears to offer particularly attractive possibilities in connection with its bearing upon the opsonic properties of the blood, which, it seems reasonable to presume, should be more or less influenced by the pronounced metabolic disturbances incident to this disease. Especially is this true of cases attended by excessive glycosuria, and of those characterized by glaring inadequacy of fat oxidization, whereby the acetone bodies accumulate unduly in the blood and in the other tissues of the body, thus rendering the subject prone to the dangers of acid intoxication. The well-recognized susceptibility of the diabetic individual to boils and carbuncles, to spontaneous gangrene, and to pulmonary tuberculosis also argues, on *a priori* grounds, some deviation from the normal opsonin values, either as a cause or as a consequence of these complications. Furthermore, one is tempted to accept as more than an alluring theory a possible relation between the opsonic function and the hormone body "secretin," which substance, having been proved by Bayliss and Starling[2] to be an active factor of pancreatic secretion, was found to exist in minimal quantities in the non-pancreatic type of diabetes by Bainbridge and Beddard,[3] and more recently has been studied by Wentworth,[4] and by Sweet and Pemberton,[5] with relation to diabetes and other states of defective nutrition.

With the foregoing premises in mind, we have thought it worth while to investigate, in a reasonable number of diabetic subjects, the condition of the hemic resisting powers, as reflected by the behavior of the opsonic and phagocytic values in the individual instance. It is aside from the main question here to interpret the significance of opsonins and their effects upon the mechanism and other phases of

[1] Read at a meeting of the Section on General Medicine of the College of Physicians of Philadelphia, March 9, 1908.

[2] Jour. Amer. Med. Assoc., 1907, xlviii, 524.

[3] Biochem. Jour., 1906, i, 429.

[4] Jour. Amer Med. Assoc., 1907, xlix, 204.

[5] Arch. Inter. Med., 1908, i, 231.

bacterial invasion, and for information about these fundamental details original sources should be consulted.[6] It is sufficient for the purposes here served to note that it is justifiable to regard opsonins as substances native to normal blood plasma which act upon various invading bacteria so as to render them easily phagocyted by the leukocytes; it is also probable that the erythrocytes are prepared for phagocytosis in an analagous manner, by the effect of the so-called "hemopsonin" of the blood; and a similar crippling of certain animal parasites—notably the trypanosome and the spirochete of relapsing fever—is believed to occur as an act preparatory to the engulfment of these microörganisms by phagocytes.

The present series of 52 cases is a supplement to the 22 reported by one of us (Da C.) a year ago, as a preliminary record of "The Opsonic Index in Diabetes Mellitus,"[7] which showed that in this disease the subject's opsonic powers are appreciably diminished, in comparison with those of a normal person, while in diabetes insipidus and in conditions of transient glysocuria no such deviation can be distinguished. The combined series of 74 cases, herewith reported, includes 50 examples of true diabetes mellitus, 4 of diabetes insipidus, 8 of non-diabetic glycosuria, and 12 of furunculosis and acne unattended by glycosuria. The data relating to this series is based upon 850 direct and control blood examinations, plus numerous repeated tests, bringing the total number of examinations close to the thousand mark. Most of the clinical material was supplied by the Jefferson, the German, and the Philadelphia General Hospitals, but for a number of referred patients we are indebted to several medical friends, especially to Dr. O. H. Petty, Dr. S. A. Munford, and Dr. J. H. Gibbon. The technical part of the work was done, through the courtesy of Prof. H. A. Hare, in his Laboratory of Clinical Medicine and Therapeutics at the Jefferson Medical College Hospital.

In the report just alluded to, it was shown that a diabetic's opsonic index to Staphylococcus pyogenes is subnormal; in this new group of 34 patients we have continued our studies with this bacterium, and, in addition, sought to determine the behavior of the blood opsonins in connection with two other varieties of bacteria, Streptococcus pyogenes and Bacillus tuberculosis. These microörganisms were selected as test-bacteria on the assumption that to such sources of infection the diabetic is peculiarly susceptible, and in this con-

[6] These contributions give the essential data and the literature of opsonins and the diagnostic and therapeutic application of the opsonic theory: Wright and Douglass, Proc. Roy. Soc., 1903, lxii, 357; Ibid., 1904, lxiii, 128, 135, 147; Wright, Lancet, 1907, ii, 423, 1213; Ross, Brit. Med. Jour., 1906, ii, 1452; Jour. Amer. Med. Assoc., 1907, xlix, 245; Crace-Calvert, Lancet, 1907, i, 279; French, Brit. Med. Jour., 1907, i, 256, 862; Ehrlich, Lancet, 1907, i, 279; Simon and Lamar, Johns Hopkins Hosp. Bull., 1906, xvii, 27; Hektoen and Reudiger, Jour. Infect. Dis., 1905, ii, 128; Potter, Ditman, and Bradley, Jour. Amer. Med. Assoc., 1906, xlvii, 1722, 1793; Miller, Ther. Gaz., 1907, xxx, 173.

[7] Amer. Jour. Med. Sci., 1907, cxxxiv, 57.

nection it may be noted that in 56 per cent. (28 cases) of our diabetic patients complications traceable to these germs existed.

TECHNIQUE. The technique used in all our estimations was essentially that of Wright,[8] with certain modifications of minor importance suggested by our increasing familiarity with the work, bred of some eighteen months experience with it. But in addition to computing merely the opsonic index to the three types of bacteria mentioned, we have also determined, in each of the new patients, the number of phagocytes in a given number of leukocytes, as well as the number of bacteria adherent to, although not actually engulfed by, the leukocytes, irrespective of their phagocytic proclivities. Thus the opsonizing properties of the blood plasma are indexed by the first process, the proportion of potential phagocytes is calculated by the second, while the last procedure may have, we fancy, some more or less close relation to the one immediately preceding.

The method of calculating the ordinary opsonic index is now so well known that it is unnecessary to recount the details in this place. Those interested will find a description of our technique in an (Da C.) article in this Journal for July, 1907.[9] It may, however, be noted that, for the sake of uniformity, only polynuclear neutrophile leukocytes were counted as phagocytes, since this rôle is so infrequently and so indifferently assumed by large mononuclear leukocytes that, to all intents and purposes, they are a negligible quantity in opsonophagocytic estimates.[10]

The richness of the blood in phagocytes was studied by ascertaining their percentage in the patients' blood, and by comparing this value with a corresponding value for normal blood (considered as 1), thus obtaining a figure that may be expressed as the "phagocytic index." Under the term "percentage index" Simon has described in detail this method of research.[11]

Our object in taking account of the attached or attracted bacteria was to discover what bearing, if any, such a condition has on true phagocytosis. Having repeatedly observed specimens of blood containing few phagocytes, but many leukocytes with numerous bacteria tightly adherent to their peripheries, this question arose: Does such a picture mean actual crippling of the cells' phagocytic powers, whereby bacteria are apparently attracted, but not engulfed; or can it be explained simply by some coincidence, or by an error in technique, such as, for example, the use of a rich, unhomogeneons culture? These questions will be discussed presently. Provisionally, the term "index of attracted bacteria" is useful to designate the figure obtained by comparing the number of leukocytes with

[8] Loc. cit. [9] Loc. cit.

[10] In less than 3 per cent.of our examinations did this type of cells figure as phagocytes, and then only in small numbers—two or three to each count of 50 leukocytes.

[11] Jour. Amer. Med. Assoc., 1907, xlviii, 139.

adherent bacteria in diabetic and in normal bloods, using 1 as the normal standard.

In the following account of our experimental work we shall analyze the results according to these three groups of cases:

I. Diabetes mellitus.
II. Diabetes insipidus.
III. Non-diabetic glycosuria.

I. Diabetes Mellitus. Of this affection 50 cases have been examined, all of which were undoubtedly true diabetes mellitus, as proved by the clinical history and by the urine analysis. In the 34 diabetics of the second series the frequency of the most prominent symptoms at the time of the blood examination may be tabulated thus:

	Per cent.	Cases.
Polyuria	91.1	31
Abnormal thirst	85.2	29
Wasting	82.3	28
Excessive appetite	70.5	24
Furunculosis	52.9	18
Pulmonary tuberculosis	29.3	10
Coma	5.8	2

Glycosuria was found in all the patients, but in none was the sugar-content excessive, ranging from as low as 0.3 per cent. to as high as 3.4 per cent. This peculiarity was probably due to the fact that the great majority of the subjects were on strict diet and systematic medical treatment, either at the out-patient clinic or in the hospital ward. Acidosis was found in 44.4 per cent. (15 cases), and albuminuria in 41.4 per cent. (14 cases) of the patients examined. No lesion of the pancreas or of the liver was found in any of the patients.

In the foregoing group the opsonic index to Staphylococcus was determined in 50, while the indices to Streptococcus and to Bacillus tuberculosis were computed in the 34 patients of the new series only. In all the latter the values relating to phagocyted and attracted bacteria were also obtained. The information derived from this inquiry makes these conclusions inevitable:

(*a*) Diabetics, as a class, have subnormal *opsonic indices* to Streptococcus, Staphyloccus, and Bacillus tuberculosis, the diminution being most striking in tests made with the first-named bacterium, well defined with the second, and moderate with the last (Chart I).

As shown by Table I, the streptococcus index averaged 44 points below the accepted normal figure, ranging between 0.38 and 1.0, and falling below 0.5 in 7 tests. The staphylococcus index, although averaging 9 points higher than this, fell below 0.5 in 16 examinations; while the tubercle index, which averaged 17 points higher than the streptococcus value, fell below 0.5 but 3 times. Comparing the most common index-range of these three bacteria

(that is, 0.5 to 1.0), a much better conception of their relative values is possible, this analysis showing these averages:

Staphylococcus: 0.66, average index for 33 cases.
Streptococcus: 0.66, " " " 29 "
Tubercle bacillus: 0.65, " " " 24 "

TABLE I.—ANALYSIS OF THE INDICES IN 50 CASES OF DIABETES MELLITUS.[12]

	Opsonic Index.			Phagocytic Index.			Index of Attached Bacteria.		
	Staph.	Strep.	T. B.	Staph.	Strep.	T. B.	Staph.	Strep.	T. B.
Average	0.65[13]	0.56	0.73	0.74	0.64	0.70	0.50	0.47	0.59
Maximum	1.44	1.00	1.73	1.18	1.04	1.33	2.64	3.00[14]	8.30[15]
Minimum	0.25	0.38[16]	0.45	0.25	0.11[16]	0.20	0.16[16]	0.10	0.10
Range of Indices.									
No. above 1.0	1	0	2	3	1	2	3	1	1
No. 0.5 to 1.0	33	26	29	26	26	25	6	10	7
No. below 0.5	16	8	3	5	7	7	25	23	26

(*b*) The *phagocytic* and opsonin values are closely parallel with Bacillus tuberculosis, the former averaging 0.70 and the latter 0.73 in 34 experiments conducted with this germ (Chart II). With Streptococcus, however, the relation is not so close, averaging as 0.64 is to 0.56; and with Staphyloccus the breach is still wider—as 0.74 is to 0.65.

These departures of the phagocytic and the opsonic indices are most difficult to explain, although most of them can safely be referred to technical defects inherent to the tests. The propinquity of the bacteria to the cells, variations in the richness of the bacterial emulsion—not to mention personal errors in technique, apparently unavoidable—are doubtless often to blame. But such questions are not germane to our subject-matter, and their discussion must raise anew the controversy as to the relative value of the act of phagocytosis, and its result as gauged by the actual number of bacteria within the cells. In passing, it may be said that neither index should be considered a strictly quantitative guide, but a qualitative figure. The value of an opsonic index relates not to the precise figure registered thereby, but rather to the finding of a decided deviation from normal; and in the moderately subnormal ranges one may not hazard a definite conclusion, although at both extremes the readings are significant.

[12] Staphylococco-index in 50 cases; streptococco- and tuberculo-indices in 34.
[13] In 34 cases of second series=0.63 for average streptococo-opsonin index.
[14] In 7 cases no attached bacteria observed.
[15] In 4 cases no attached bacteria observed.
[16] In 3 cases no phagocyted streptococci found; no attached bacteria.

(*c*) The *index of attached bacteria*, or those adherent to the periphery of the leukocytes, was studied with especial care in 34 bloods, in the hope of discovering some connection between this phenomenon and that of phagocytosis (Chart III). But the variations in our results were so wide that it is impossible definitely to associate the two processes: some actively phagocytic bloods contain leukocytes with no adherent bacteria whatever, while in others just the opposite

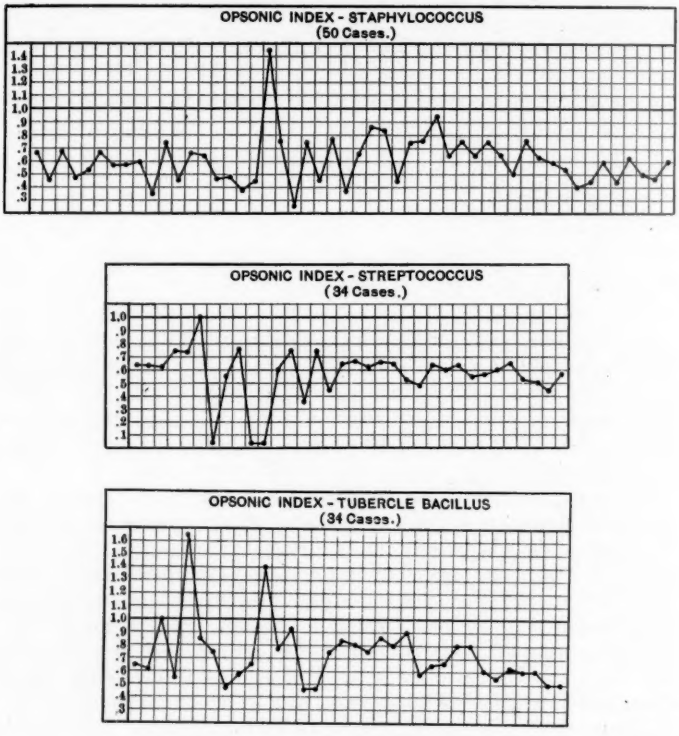


CHART I.—Opsonic indices in diabetes mellitus.

is observed. It is tempting to explain the former circumstance by assuming therein an extraordinary leukocytic defence, and the latter by assuming deficiency of this power, although it is saner to reject both hypothesis, leaving the question open to discussion. Three facts, however, were brought out by studying this detail of the attached bacteria: (1) That of the three different bacteria employed, tubercle bacilli were most frequently found clinging to the leukocytes, and, as a rule, doing so in far greater numbers than either strepto-

cocci or staphylococci; (2) that in the lower ranges (below 0.5) the uniformity of the index for all three bacteria was practically constant, differing, but very slightly, in favor of the tubercle bacillus; and (3) that to a somewhat less degree the same is true of the range of averages between 0.5 and 1.

The points referred to in the three preceding paragraphs are well illustrated by Table I, and in the accompanying charts the individual ranges of the three different indices are shown.

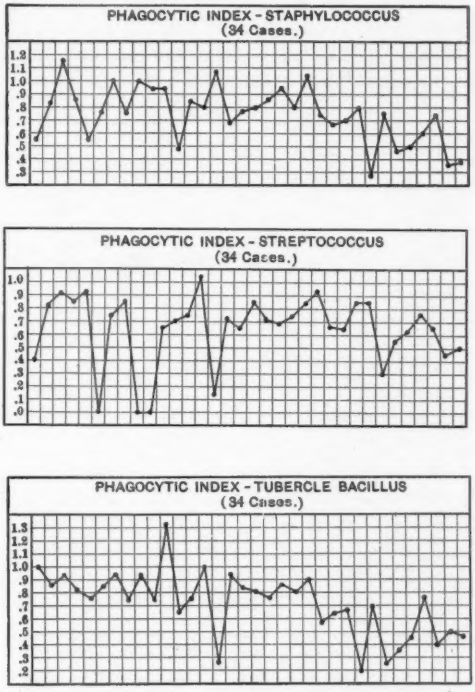
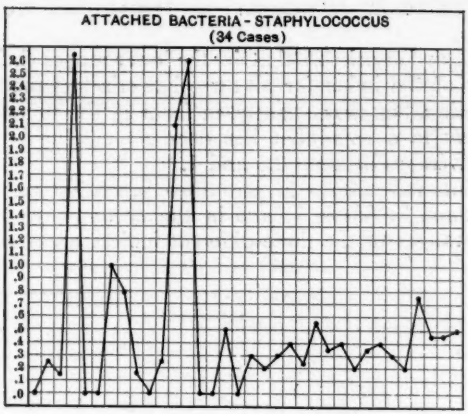
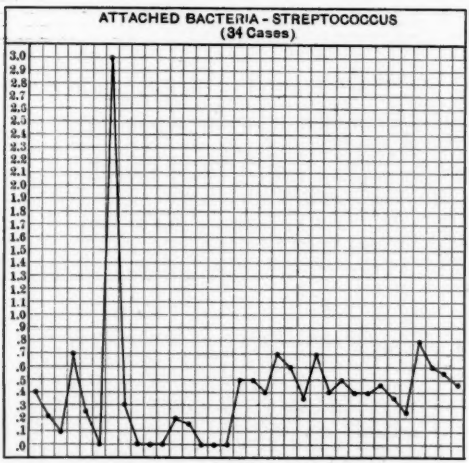


CHART II.—Phagocytic indices in diabetes mellitus.

(*d*) *Influence of Complications.* Thus far we have considered diabetics as a class, aside from which there remain numerous cases to be reviewed comparatively, owing to the existence of certain well-marked attendant or complicating conditions. To this class, then, belong those with acidosis, those suffering from furunculosis, and those affected with tuberculosis of the lungs.

In the group of *diabetes with acidosis* are included 15 patients whose urine contained acetone, diacetic acid, or both, in appreciable





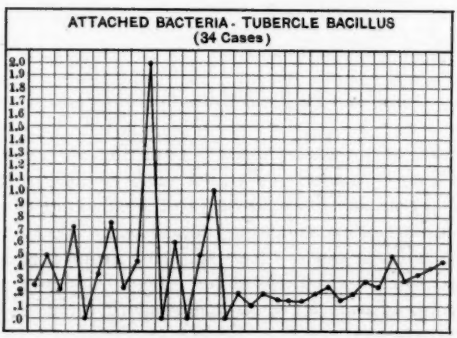


CHART III.—Indices of attached bacteria in diabetes mellitus.

amount at the time of the blood examination.[17] The term "acidosis" is used, therefore, in a somewhat loose sense, rather than necessarily to denote frank acid intoxication, perhaps amounting to coma, which was present in but two instances.

In dealing with this class of examinations one is forcibly impressed with two findings: the unduly low tubercle indices, both opsonic and phagocytic, in comparison with similar figures for cases without acidosis; and the virtually constant correspondence of the streptococcus and staphylococcus values in the two groups of patients.

Thus, the tuberculo-opsonic index averaged 23 points lower, and the tuberculophagocytic index 19 points lower, in acidosis cases than in the non-acidosis class. Even the questionable index of attracted bacteria declined in a most extraordinary degree—62 points for tubercle, and from 30 to 40 for the other bacteria. With reference to these findings it is important to note that but 2 of the low tuberculo-indices were found in tuberculous subjects affected with acidosis (Cases XXV and XLVII), and in neither was the value of such a nature as materially to affect the averages calculated for the complete acidosis series. In contrast to these deviations, the acidosis group of opsonic and phagocytic indices to the pyogenic cocci closely agreed with like values for patients without acidosis, the two differing not more than 4 points, save in the streptococcus phagocytic index, which ran 10 points lower in the acidosis class.

Of the 2 patients with *diabetic coma*, the urine of the first (Case III) contained both acetone and diacetic acid, and the urine of the second (Case XV) only acetone. In the first instance the opsonic values were 0.44, 0.61, and 0.51 to Staphylococcus, Streptococcus, and Bacillus tuberculosis, respectively; while in the second instance the corresponding values read 0.77, 0.45, and 0.46. In both patients the disease was of the acute type, and in the first one it proved fatal within a fortnight after the subject first came under observation.

This table of averages in diabetes with and without acidosis is illustrative of the decided differences here existing.

TABLE II.—DIABETES MELLITUS WITH ACIDOSIS.

	19 cases without acidosis.[18]	15 cases. with acidosis.
Opsonic index.		
Staphylococcus	0.59	0.63
Streptococcus	0.63	0.60
B. Tuberculosis	0.89	0.66
Phagocytic index.		
Staphylococcus	0.82	0.80
Streptococcus	0.74	0.64
B. Tuberculosis	0.86	0.67
Index attached B.		
Staphylococcus	0.71	0.30
Streptococcus	0.63	0.33
B. Tuberculosis	0.92	0.30

[17] Lieben's and Gerhardt's tests were used in the routine examinations for acetone and diacetic acid, respectively.

[18] Staphylococco-opsonin index in 35 cases; all others in 19.

Furunculosis was present in 18 of the diabetic subjects, but, aside from certain minor details, this complication seems, *per se*, to have no material effect upon either the opsonic or the phagocytic power of the blood. In furunculosis cases, as well as in those with a clean skin, these averages were not dissimilar, save for a relatively feeble phagocytic action toward the staphylococcus and a comparatively vigorous attack upon the streptococcus, in the former group. In all the experiments it appeared that the combative powers of the leukocytes outstripped their destructive capacity for the bacteria attacked, since the phagocytic index consistently ran somewhat higher than the opsonic figure. The low range of the tubercle index of attached bacteria (45 points subnormal) is here almost as conspicuous as in the acidosis group. Table III demonstrates this peculiarity, as well as the other details just described.

TABLE III.—COMPARATIVE AVERAGE VALUES IN DIABETICS WITH AND WITHOUT FURUNCULOSIS.

	18 diabetics with furunculosis.	16 diabetics without furunculosis.
Opsonic index.		
Staphylococcus	0.62	0.59
Streptococcus	0.59	0.52
B. Tuberculosis	0.69	0.77
Phagocytic index.		
Staphylococcus	0.67	0.82
Streptococcus	0.73	0.53
B. Tuberculosis	0.71	0.78
Index attached B.		
Staphylococcus	0.50	0.51
Streptococcus	0.40	0.55
B. Tuberculosis	0.36	0.91

Apropos of the above results (Table III), it may be noted that in 4 non-diabetic patients with furunculosis the opsonic index to Staphylococcus averaged only 0.45; while in 8 cases of pustular acne (also non-diabetic) the average indices were 0.50, 0.95, and 1.03 to Staphylococcus, to Streptococcus, and to Bacillus tuberculosis, respectively. These data, although limited, emphasize the great decline of the tuberculo-indices in diabetes complicated by furunculosis, in comparison with similar values found in non-diabetic persons affected with pustular lesions.

In *diabetes complicated by pulmonary tuberculosis* both opsonic and phagocytic indices averaged practically the same as those of non-tuberculous diabetics, except for a five-point and a twelve-point variation with the streptococcus. This can probably be disregarded, in view of the trifling differences involved, and because of the consistent uniformity of the other estimates. It is of some interest to find that in tuberculous diabetics the tuberculo-index of attached bacteria falls as it does in acidosis cases, although the average decline is some 11 points less than in the latter. The behavior of the several index averages in tuberculous and non-tuberculous patients is shown by Table IV.

TABLE IV.—DIABETES MELLITUS WITH PULMONARY TUBERCULOSIS.

	24 non-phthisical cases.[19]	10 phthisical cases.
Opsonic index.		
Staphylococcus	0.62	0.61
Streptococcus	0.55	0.60
B. Tuberculosis	0.73	0.75
Phagocytic index.		
Staphylococcus	0.74	0.74
Streptococcus	0.62	0.74
B. Tuberculosis	0.68	0.69
Index attached B.		
Staphylococcus	0.49	0.54
Streptococcus	0.42	0.60
B. Tuberculosis	0.71	0.41

(*e*) *Influence of Glycosuria.* The relation between the *degree of glycosuria* and the opsonophagocytic action was investigated in every case belonging to the second series, of which 18 had a sugar-content below 5 grains to the ounce, while in 16 this figure was exceeded, the average amount of sugar being 2.1 grains in the first, and 8.3 grains in the second, group.[20] Comparison of these groups admit of but one deduction: that a *high* degree of glycosuria implies a *low* grade of bacterial resistance, while with a moderate glycosuria the index is unquestionably higher. This is emphatically true of the tuberculo-indices, which in patients with a low sugar content showed an opsonic index 29 points higher, and a phagocytic index 33 points higher, than the corresponding value for subjects having a high content of sugar.[21] And here, as in the other cases referred to, the peculiar behavior of the tubercle index of attached bacteria attracts attention, for this value differs no less than 39 points in favor of the "low sugar" group of patients.

TABLE V.—INFLUENCE OF GLYCOSURIA ON THE INDICES.

	18 low sugar cases.[22]	16 high sugar cases.[23]
Opsonic index.		
Staphylococcus	0.66	0.62
Streptococcus	0.69	0.55
B. Tuberculosis	0.89	0.60
Phagocytic index.		
Staphylococcus	0.82	0.76
Streptococcus	0.78	0.64
B. Tuberculosis	0.93	0.60
Index attached B.		
Staphylococcus	0.45	0.64
Streptococcus	0.64	0.36
B. Tuberculosis	0.81	0.42

[19] Staphylococco-opsonin index in 40 cases; all others in 24.

[20] Fehling's and Böttger's tests were used for glucose, and in doubtful reactions, the fermentation and the phenylhydrazin tests.

[21] The adjectives "low" and "high" here refer to the two degrees of glycosuria above alluded to—those below and those above 5 grains to the ounce.

[22] Four cases with acidosis.

[23] Seven cases with acidosis.

So far as we were able to determine, *albuminuria* is not to be regarded as a factor of index deviations. Nor could any correspondence be recognized between the *leukocyte count* and the phagocytic activity of the cells.

II. Diabetes Insipidus. In 4 cases of diabetes insipidus opsonic indices of 0.82, 0.82, 0.87, and 0.89 to Staphylococcus were found, or values ranging within normal limits, which vary from 0.80 to 1.2, according to Bulloch's studies of 84 healthy subjects.[24] The foregoing cases belong to the first series reported, in which only the staphylococco-opsonic index was investigated, and having met with no more examples of this disease during the past year, we are denied the opportunity of recording the behavior of the phagocytic percentage and the index of attached bacteria in non-saccharine diabetes. On clinical grounds, it is unlikely that there is any deviation from normal, although no actual proof of this presumption is at hand.

III. Non-diabetic Glycosuria. In 8 patients with transient glycosuria all the index values, collectively and individually, were well within the normal range, except in the last 3 tests with Streptococcus, which showed moderately subnormal opsonic indices (0.70, 0.76, and 0.75), with most divergent values for phagocytes. This we regard as a discrepancy due to the use of an unsatisfactory streptococcus culture, with which bacterium, it may be added, we have had considerable trouble at different times. This being the case, we prefer to draw no conclusions from the streptococcus values in the cases under discussion, and figures relating to this germ are stated with this proviso.

With the other bacteria consistently high values were obtained, ranging some 20 to 30 points higher than similar values for diabetes mellitus. Although 8 records are scarcely comparable with 50, we tabulate the averages of non-diabetic glycosuria with those of diabetes mellitus, in view of the striking contrast thereby shown.

Table VI.—Glycosuria versus Diabetes.

	8 glycosuria cases.	50 diabetic cases.
Opsonic index.		
Staphylococcus	0.96	0.65
Streptococcus	0.81 (?)	0.56
B. Tuberculosis	0.98	0.73
Phagocytic index.		
Staphylococcus	1.01	0.74
Streptococcus	1.02 (?)	0.64
B. Tuberculosis	0.93	0.70
Index attached B.		
Staphylococcus	0.79	0.50
Streptococcus	0.62 (?)	0.47
B. Tuberculosis	0.54	0.59

[24] Trans. Path. Soc., London, 1905, lvi, 334.

CONCLUSIONS. With no sacrifice of logic, we believe that the following deductions are warranted by the clinical and laboratory findings herewith reported:

1. In diabetics, as a class, the resisting powers of the blood against bacterial infection are conspicuously subnormal, in comparison with a similar hemic property in the healthy individual. As measured by the opsonic index, the average diabetic's resistance is approximately one-third below normal, and, in the exceptional case, reduced more than two-thirds. This applies to infections by the streptococcus, the staphylococcus, and the bacillus of tuberculosis, whose relative predilection for the diabetic is expressed by the order given.

2. The higher grades of diabetic glycosuria are attended by a feebler opsonophagocytic action than the lower grades, and the reverse of this also is true. This deficiency is particularly striking in the case of the tubercle bacillus.

3. Diabetic acidosis particularly lowers the blood resistance to the bacillus of tuberculosis, but a less degree of vulnerability appears to exist with regard to the streptococcus and the staphylococcus.

4. Diabetic furunculosis does not materially depress the subject's opsonophagocytic powers to the ordinary pyogenic cocci below the figures usually incident to this disease.

5. Diabetics affected with pulmonary tuberculosis show virtually the same resisting powers as do subjects of uncomplicated diabetes.

6. In non-saccharine diabetes the opsonic values to the staphylococcus range within normal limits, and this statement also applies to non-diabetic glycosuria.

In conclusion, we would advise the use of the opsonic test in diabetes mellitus as a means of gaging, in a general way, the extent to which the subject's vitality is undermined, and for this purpose the test is especially useful in patients threatened with acid intoxication, and in those having excessive glycosuria. Systematic opsonic records in an average case of diabetes reflect most clearly the inroads of this affection, as well as the patient's behavior under the stress thereby imposed. Of this we have ample proof, in numerous patients in whom repeated examinations were made, over extended periods of time. In this connection also, the opsonin test, hitherto studied only in its relation to infectious processes, should be useful in the investigation of several other conditions—gout, rickets jaundice, and cachexias consequent to chronic nephritis, hepatic cirrhosis, malignant disease, and severe anemia.

THE BLOOD PRESSURE IN ARTERIOSCLEROSIS.

By R. D. Rudolf, M.D., C.M. (Edin.), M.R.C.P. (Lond.),
ASSOCIATE PROFESSOR OF MEDICINE IN THE UNIVERSITY OF TORONTO, TORONTO, CANADA.

It has long been known that in cases of thickened arteries the blood pressure is likely to be raised. This increased pressure used to be recognized only by the fingers of the examiner, and was referred to as the "tension between the beats." During the last few years, however, many instruments have been introduced for accurately measuring this pressure. Most of these measure not the tension between the beats at all, but the force of the pulse wave, or, as it is termed, the "systolic pressure." A few, such as that of Erlanger, gauge the pressure between the beats, or, as it is called, the "diastolic pressure;" but most work has been done upon the systolic pressure, which is practically the force of the left ventricle. P. M. Dawson[1] has shown conclusively that the best measure of the systolic output of the heart is the pulse pressure, that is, the difference between the diastolic pressure and the systolic pressure. A patient may have an abnormally high systolic pressure and yet have a dangerously low pressure between the beats, as was the case in a woman examined recently who was dying of aortic regurgitation and yet her systolic pressure was 170 mm. Hg.; her still abnormally strong heart was pumping blood into a comparatively empty arterial tree.

My work has been mostly done with the Martin and the Janeway sphygmomanometers, both of which are modifications of the Riva-Rocci instrument. The former only registers the systolic pressure; the latter is supposed to give also the diastolic pressure, but in my hands at least is very unsatisfactory in this respect. I venture to express the belief that it is the diastolic pressures that we most require to know, and I think that there is great need of a portable instrument that will meet this want.

Although the sphygmomanometer is often of the greatest value in making accurate measurements of blood pressure, the importance of estimating the blood pressure—both systolic and diastolic—by the trained finger is as great as ever, and in many cases is all that is necessary. In the majority of cases, with a little practice, one can even come very near to the systolic pressure in millimeters of mercury by the trained touch alone. The cases in which one is most likely to err are those of very high pressure; it is very difficult, for example, to measure the pressure of a pulse above 200 mm. In arteriosclerosis the first rise that may occur is in the pressure between the beats, and the left heart, as a consequence, becomes stronger than normal, and its amount of hypertrophy is a good gauge of the degree of pressure that it has had to work against.

[1] Brit. Med. Jour., October 20, 1906.

At one time increased arterial pressure was spoken of as a constant accompaniment of arteriosclerosis, but now that actual measurements can be made, it is found that frequently this pressure is normal or even below normal in such cases. Dunin[2] measured the blood pressure 1000 times in 440 patients with arteriosclerosis in his private practice. He used Gaertner's tonometer in his work. In 120 out of the 440 arteriosclerotic people (27.5 per cent.) the pressure was normal or low. Groedel,[3] of Nauheim, recently published measurements in 500 cases of well-marked arteriosclerosis. In 35 per cent. he found no increase in pressure. Many other workers have come to the same conclusion, and as far as one's small experience warrants, the conclusion is the correct one. Last winter Messrs. A. Ellis and L. B. Robertson, senior medical students in the University of Toronto, investigated this point for me in the General and St. Michael's Hospitals, and their results show that only in about half of the well-marked cases of arterial thickening examined did the pressure run above normal. Occasionally we find a low pressure, when, from the enlargement of the left heart, etc., it is evident that at last the heart is giving up its struggle against long-continued, high pressure. Such a case as the following illustrates this point: A tall, thin man came complaining of great dyspnœa and other signs of cardiac insufficiency. His vessels were markedly thickened and tortuous, and the cardiac apex was felt in the sixth left intercostal space outside the nipple line, and yet the pulse could scarcely be distinguished at the wrist. He was near his end.

Granting that there are many cases of well-marked arteriosclerosis in which the blood pressure is at or below normal, and apparently has never been otherwise, how can we account for the apparent discrepancy? It must be remembered that it takes a great deal of interference with the arterial tree before there is any alteration in the general blood pressure. One may, for example, ligate a large artery, such as the femoral or the common carotid in the dog, without producing any long-continued rise in the general pressure. It is probable that in many of the cases of well-marked sclerosis of the radials the pressure is not raised because the rest of the arterial tract is normal. Localized sclerosis of the splanchnic vessels, however, is said more easily to give rise to increased arterial pressure than is the same amount of disease elsewhere, these vessels being intimately connected with the regulation of the general blood pressure. Hasenfeld and Hirsch, according to Janeway,[4] have definitely proved that arteriosclerosis only leads to increased blood pressure and hypertrophy of the left ventricle when the splanchnic vessels or the aorta above the diaphragm are highly diseased.

[2] Ztschr. f. klin. Med., liv, Nr. 4.
[3] T. Clifford Allbutt, Brit. Med. Jour., October 20, 1906.
[4] The Clinical Study of Blood Pressure, p. 143.

During some experimental work on blood pressure done some time ago in the Physiological Department of the University of Toronto[5] I came to the conclusion that, while the splanchnic vessels are all-important in the maintaining of blood pressure, yet the vessels below that point are also of great value in the same way; and I should much like to hear of a case of marked sclerosis of the arterial tract below the origin of the splanchnic vessels, and with these vessels normal, in which there was a normal arterial pressure.

When, in a case of arteriosclerosis, we find the pressure to be high, it is necessary to find out how much of this hyperpyesis is due to the disease of the vessel walls and how much to other causes. Careful and repeated examinations of the urine will help toward finding if the condition is due in whole or in part to disease of the kidneys. There may be, and frequently is, a vasomotor element in the case due to toxic or nervous influences, and the free use of the nitrites will assist in gauging the amount of this factor present, the pressure falling much more in such cases than when the pressure is due solely to sclerosis of the vessel walls. Sir Clifford Allbutt[6] writes that "it is a remarkable experience that in cases of great involutionary deformity of the vessels, or, at any rate, of those that are palpable, intercurrent attacks of hyperpyesis may be detected, estimated, and dissipated with as much ease as in persons not so affected."

The question suggests itself here of how much of the normal pressure is dependent upon the activity of the suprarenal capsules. If these are normally active, other influences being undisturbed, the arterial pressure will remain normal. If, however, the suprarenals be sluggish, then the pressure should remain low, and, on the other hand, if they be overactive it should be raised. We know of variations in the functional activity of so many other glands of the body that the conclusion seems almost inevitable that in many cases of disturbed blood pressure we are dealing with examples of over- or under-activity of the suprarenal glands. This interesting question was very ably discussed by Dr. H. D. Rolleston[7] at the last meeting of the Canadian Medical Association, at Montreal.

On the whole, one may say that the finding of a heightened blood pressure is of some value in the diagnosis of a widespread arteriosclerosis, but that, on the other hand, a considerable and often very serious degree of the disease may exist with a normal pressure. I have studied many cases of the latter class in the last few years. One such case much impressed me recently. It was that of a professional man, aged forty-six years, who, after an abstemious but strenuous life, began at the age of forty-three years to suffer from angina pectoris. His right radial was markedly sclerosed, but not so the left or either brachial artery. The blood pressure, upon re-

[5] Observations on Blood Pressure, Univ. of Toronto Study, No. 3.
[6] Loc. cit.
[7] Canada Lancet, November, 1907.

peated examination between the attacks, never ranged above 145 mm. The urine was normal. He died in an anginous attack, and the post-mortem examination revealed very marked sclerosis of the coronary arteries, but little disease of the rest of the arterial tree. Another case comes to mind—that of a clergyman, aged sixty-three years, who died of slow cerebral thrombosis. His grandfather had died of apoplexy at seventy years, and the father at sixty-seven years of some similar condition. In this case the arteries open to palpation were not sclerosed beyond what is normal at sixty-three years and the blood pressure was not raised. He had lived a most abstemious life, except as regards "high thinking."

The rise in pressure in cases of sclerosis is usually attributed to the resistance to the onward flow of blood produced by the sclerosed arterial walls. But it is in some cases due possibly to quite a different mechanism. Kocher and Cushing showed some time ago that in localized anemic conditions of vital parts of the brain the blood pressure rises enormously, this rise being evidently an endeavor upon the part of the body to force blood into the dangerously blanched areas. Cook and Briggs[8] also illustrate this well by a chart showing the blood pressure in a case of hemorrhage upon the surface of the brain. The pressure was 360 mm., and after the removal of the clot it fell and remained at normal. Recently a somewhat similar case came under observation: A lady, who had been well except for frequent headaches and some slight hesitation in speech, became for the third time this winter rather suddenly unconscious with signs of acute cerebral compression. During the attack her pressure rose from 125 to 210 mm. Next day, although still profoundly unconscious, with fixed pupils and Babinski's sign in both feet and other signs of marked pressure, her blood pressure was found to be 135 mm. This sign helped one to surmise that the cerebral compression was lessening, and within twelve hours she was quite conscious and is now practically well. These are illustrations of acute compensatory rises in blood pressure, but it seems altogether likely that if the circulation in vital parts of the brain is interfered with by arterial sclerosis, the general blood pressure will rise in the same way in order to get blood into the needful parts.

With the general treatment of arteriosclerosis one is not here concerned, but it may not be out of place to mention a few points from the blood pressure point of view. It is in what has been called the pre-sclerotic stage of the disease that most may be done to relieve the condition. One would fully endorse Sir Clifford Allbutt's sound advice that every adult of say forty-five years and over should, at intervals of two or three years, have his blood pressure taken, in the hope that it may guide his physician to use every endeavor to postpone or prevent the onset of arteriosclerosis. Not that an

[8] Clinical Observations on Blood Pressure, Johns Hopkins Hospital Reports, 1903, vol. xi.

increased pressure will inevitably produce sclerosis, although if continued long enough and be high, it may do so, but increased pressure and damage to the vessel walls may both be due to some toxin that can, by careful living and treatment, be lessened. In such cases, if we adopt measures such as restricted diet, increased elimination, and the use of the iodides, we may keep the pressure down and are probably at the same time lessening the toxemia which will soon lead to irritation and consequent sclerosis of the vessel walls. It is not advisable in every case of arteriosclerosis immediately to resort to strong measures, such as the nitrites, in order to lower an abnormally high blood pressure. The tissues supplied by the thickened arteries, and it may be vital tissues, are only able to get enough blood for their uses when the pressure is abnormally high.

It is wonderful what apparently good health many of these arteriosclerotic people enjoy, even when their pressures are very high. Such a case as the following is of every-day occurrence: A lady, aged fifty-eight years, feels well, except for some breathlessness on exertion and an occasional sense of oppression in the chest. The urine is normal and the arteries moderately sclerosed. Her systolic pressure is constantly between 220 and 235 mm. She has an occasional numbness in the left arm and frequently is dizzy, but does not suffer from headaches. In my experience headaches are not common in arteriosclerotic cases in which the urine remains normal, and I note with interest that G. L. Walton and W. E. Paul[9] recently found, in an analysis of 100 cases of arteriosclerosis, that headache was only present in 22 per cent.

Arteriosclerotic patients often feel weak and shaky and, with the idea of keeping up their strength, take more food than they would use in health. Such a patient came to me about three years ago. Her blood pressure was 240 mm. She was nervous, depressed, and suffered from some headache, and, with the wrong idea that the condition was due to want of nourishment, was taking three good meals a day with lots of meat and eggs, and between meals frequent cups of strong beef tea and sips of whisky. Under a restricted diet, with free saline laxatives and small doses of iodide of potassium, her pressure came down to 190 mm., and she felt much better and the desire for extra food left her. She kept thus fairly well until last month, when she had a hemiplegic attack, and then the urine for the first time was found to be albuminous and the blood pressure over 200 mm.

The onset of early arterial sclerosis should be specially looked for and as far as possible prevented in those individuals whose family history shows that they have a tendency to the disease. Personally, I have seen more cases of the disease in those who have lived abstemious lives than in those who have indulged too freely in the

[9] Jour. Amer. Med. Assoc., January 18, 1908.

pleasures of the table. In many such cases the only fault that can be found is the strain and stress of modern life acting upon individuals in whom, as Osler graphically puts it, bad material was used in the make-up of the vascular machine.

CONCLUSIONS. 1. In many cases of even well-marked arteriosclerosis the blood pressure is not raised. This may be because the disease is localized to a part of the arterial tree, or because the heart may at last be giving up the struggle and hence the pressure, once high, has now fallen.

2. In many cases of arteriosclerosis the blood pressure is above normal.

3. In a given case of arteriosclerosis, in which the pressure is found to be raised, it cannot be assumed that the pressure is high because of the disease of the vessel walls, nor yet that the sclerosis is due to the increased pressure. For example, the arterial stiffening may be due to syphilis, and the hyperpyesis to some intercurrent condition of nervous or toxic nature which may be more or less removable by appropriate treatment.

SYMPTOMS ATTRIBUTED TO THE MYOCARDIUM IN REALITY OFTEN OF PERIPHERAL ORIGIN.

BY LOUIS FAUGERES BISHOP, A.M., M.D.,

CLINICAL PROFESSOR OF HEART AND CIRCULATORY DISEASE IN THE FORDHAM UNIVERSITY SCHOOL OF MEDICINE, NEW YORK CITY; PHYSICIAN TO THE LINCOLN HOSPITAL, NEW YORK.

THE progress of medical thought has always been one of differentiation whereby a group of symptoms which at the time stands for a supposed entity is after a while divided to represent two different conditions, and these are again subdivided, until finally, in place of one disease with a very complex group of symptoms, there is a number of simpler ones with fewer symptoms. Thus, typhus fever once covered typhoid fever, what is now known as typhus fever, and a number of other febrile conditions which have since been more definitely placed. Rheumatism also has been differentiated into a good many conditions which now present no difficulties of distinction.

The same thing is about to happen to that group of heart conditions which has been called myocarditis, corresponding to a predicated organic disease of the heart muscle, which was supposed to produce certain symptoms. It has been customary to attribute many sudden deaths to this condition, while, in fact, it is not logical to believe that a disease characterized by destruction of muscular tissue should terminate suddenly without previous manifestation of muscular weakness. I should be willing once for all to rule out

from the group of pure myocardial disease all those cases in which there is no sign of myocardial weakness, as shown by the inability of the heart to develop extra muscular force, when such force is needed; in other words, cases in which action of the heart responds to the demands of exercise, in which there is no dyspnœa when the physiological activities of the body are increased, as during digestion, or at night when the blood tension is higher, and those cases in which there is no failure of the proper circulation of the blood in any part of the body, not even the liver, which is often the first to suffer.

Again, I should rule out as true myocarditis those cases in which there have been gross departures from normal in the peripheral circulation, such as extreme high tension that has led to hypertrophy and exhaustion of the heart muscle, for in these cases, when relieved of the outside attacks upon its integrity, the heart muscle often shows wonderful recuperative powers. Again, I should like to express the belief that in the undoubted cases of myocardial degeneration due to infectious diseases, many of the symptoms are really due to a coincident degeneration of the peripheral vasomotor mechanism, and if this can be regulated the heart muscle will be found quickly to regain a sufficient tone to answer reasonable demands. In diptheria particularly the well known tendency of the toxin to attack the nervous mechanism makes it seem more than likely that the muscular fibers of the heart may after all not be the most important elements involved. The heart muscle is one of the most tolerant structures in the human body, and has carried the odium of many accidents which never belonged to it.

I do see a certain number of cases which seem to me to be true myocarditis, but as my attention has been more and more drawn to the circulation as a whole, not neglecting its peripheral vessels and nervous control, these cases have become fewer and fewer. The name arteriosclerosis, taken in its broader, modern sense of disorder of the bloodvessels (the best name we have, but not a good one), would more truly cover many cases that have been attributed to myocarditis. An individual who has been subject to general toxic conditions, disease, indiscretion of diet, or some specific poison or intoxication, is found with a pulse irregular in force and rhythm, attacks of dizziness, and perhaps tinnitus. The heart is free from murmurs, there is no particular dyspnœa on exertion, the arterial tension is low, there is no congestion of the liver and no œdema of the extremities. Such a case I believe to be ordinarily a case in which the true lesion is to be found principally in the circulatory mechanism located in the nerves and vessels outside of the heart.

On the other hand, a patient shows the same irregularity, or perhaps no irregularity at all, in the pulse, hypertonicity of the bloodvessels (through an attempt of the vessels to compensate for the weak heart), congestion of the liver, dyspnœa on exertion, slight œdema of the feet; I should not hesitate to say that that patient

is suffering from a true weakness of the heart muscle. So I must confess that a study of the circulatory disease has led me almost to a reversal of my original conception of the symptomatology of myocarditis. This train of thought, principally started by the apparent inconsequence of the outcome of these cases, and continued later by reflection on the results of the experimental destruction of the heart muscle as observed in the experimental laboratory and on the relation of blood pressure study in these cases, has made me prepared at the present time to change my views.

There is something more to be learned as to blood pressure in its relations to vascular tone and the movement of blood in the vessels, and I hope the time will soon come when we shall be prepared to make a better classification of blood pressure symptoms. To this end the routine use of the sphygmomanometer, while not allowing its findings to cover the whole surface of the clinical picture, is important.[1]

A true myocarditis with its characteristic symptoms is seen in acute syphilitic inflammation of the heart muscle. In such cases, with absolute irresponse of the heart muscle to physical and physiological demands, may be found the fundamental symptoms of myocarditis. When the heart sounds can be heard satisfactorily, murmurs are likely to accompany myocarditis. Murmurs arise so quickly from dilatation of one part or another of the heart, such as logically exist if the heart muscle is markedly deficient, that it is difficult to believe in the existence of myocarditis where the sounds of a forcibly acting heart are present without murmurs, although some very recent writers believe in such myocarditis.

PERSISTENT PATENCY OF THE DUCTUS ARTERIOSUS.

By H. Gideon Wells, M.D.,
Assistant Professor of Pathology in the University of Chicago, Chicago.

Persistent patency of the ductus arteriosus has been the topic of several extensive articles, but in reviewing the literature in connection with the study of a case that I recently had the fortune to examine postmortem, it was found that there is practically no systematic discussion of the topic in the English literature, and that none of the reports is complete in the light of recent developments. Therefore, although the occurrence of a patent ductus arteriosus in an adult, which gives rise to symptoms during life and is demonstrated at

[1] In these studies I now use the hydrostatic instrument, which will be found described in the appendix (1908) of Wood's Reference Handbook of the Medical Sciences, in the article on "Arteriosclerosis."

autopsy, is of itself so uncommon as to call for study and publication, it would seem also to be desirable to review rather completely the entire subject as it stands at the present time. Among the best systematic discussions are those of Rauchfuss[1] (1859), Gerhardt[2] (1867), Wraný[3] (1871), Vierordt[4] (1898), and Gérard[5] (1900); but since the first three of these were written the work of Zuntz[6] and Strassman[7] seems to have explained satisfactorily the mechanism of the normal closure of the ductus arteriosus and to have thrown an entirely new light upon the subject, while in the articles of Vierordt and Gérard this work is not taken into account. Later articles in which the studies of Zuntz and Strassmann have been considered, by Roeder[8] (1900) and Wagener[9] (1903), are particularly concerned with certain features of this subject and do not discuss it in a comprehensive manner.

The case that I have to report concerns a patient in the service of Dr. Charles Mix at the Cook County Hospital. The history is obtained from the notes of the internes, Drs. Moes and Grisinger, in whose charge he was. The man was aged forty-two years, born in Sweden, and occupied as a general laborer in a piano factory. He entered the hospital on account of severe icterus and pronounced cholemic manifestations, which suggested the possibility of the presence of occlusion of the common duct by a malignant growth. This cholemic condition persisted during the eight days he was under observation before death, and as the liver seemed to be small, and it was found that there was no constant obstruction to the entrance of bile to the intestine, acute yellow atrophy was suspected. Death occurred on July 10, 1907, after a sudden rise of temperature to 106°, and some hemorrhage from the bowel.

The previous history of the patient was negative; he denied any previous illnesses, and apparently had never been in any way affected by the condition of the heart and vessels, at least not enough to attract his attention to them. The cause of the death of his parents was unknown; he had one brother and one sister living and well. He admitted drinking considerably of both alcoholic and malt liquors. Examination of the heart at the time of entrance was made, and the notes on the history sheet are as follows: The apex beat is diffuse as seen and felt in the sixth interspace just inside the nipple line. The area of cardiac dulness reaches to the upper border of the fourth rib above and a finger's breadth outside the

[1] Virchow's Archiv, 1859, xvii, 376.
[2] Jena Zeitschr. f. Med. u. Naturwissenschaft., 1867, iii, 105.
[3] Oesterreiches Jahrb. f. Pädiatrik., 1870-1871.
[4] Nothnagel's System, 1901, xv, Pt. 2, 155.
[5] Revue de méd., 1900, xx, 645 and 837; Jour. d. l'Anat. et Physiol., 1900, xxxvi, 1 and 323; 1903, xxxix, 1.
[6] Pflüger's Archiv, 1888, xlii, 342.
[7] Arch. f. Gynäkol., 1894, xlv, 393.
[8] Arch. f. Kinderheilk., 1900, xxx, 157; Virchow's Archiv, 1901, clxvi, 513.
[9] Deut. Arch. f. klin. Med., 1903, lxxix, 90.

nipple line, with impaired percussion note to the anterior axillary line; it reaches the right border of the sternum to the right. The impulse is very strong in the apical region, and "it almost seems as if there were a thrill there." The sounds at apex are very loud, and the first sound is impure. A murmur is heard in the second right interspace which is quite loud and blowing, systolic in time, and also heard in the second and third left interspace; the second sound is accentuated. The heart misses a beat at long intervals. A note by another examiner two days later also notes the murmur in the second right interspace, and records the absence of any palpable thrill. Two days befo e death the following note was made: Dulness extends one inch to the right of the sternum in the second interspace; a systolic murmur is heard here, and down along the right border of the sternum; the second sound is accentuated; there is no thrill; the heart beats are rather forcible. A distinct systolic murmur is heard in the sixth left interspace.

As can be seen, the predominant feature in this case was the icterus and cholemia, the cardiac findings being secondary; these were, however, such as to impress the examining physicians as being different from the ordinary heart lesions, and a tentative diagnosis of dilatation of the aorta was made. As will be seen later, the dulness in the right second interspace is a prominent feature of patency of the ductus arteriosus, and the murmur as heard was of a suggestive character.

A summary of the findings at the autopsy follows:

The body is that of a small, fairly well nourished and developed man, extremely icteric. There are several small subcutaneous lipomas on the right forearm. The abdominal cavity shows no changes except for a small left inguinal hernia. The diaphragm is at the normal level. The liver is three fingers' breadth above the costal margin, its size considerably decreased, the weight being but 1100 grams; it is a deep yellow color, consistence flabby, and there are numerous subperitoneal ecchymoses. The gall-bladder is moderately distended, all the large ducts are patent, and there are no concretions. The cut surface of the liver is very yellow, and there is an evident increase in the connective tissue about the lobules. Microscopically there was found in this liver a pronounced multilobular cirrhosis, with severe icterus and icteric necrosis, plus fatty changes. The lungs show subpleural hemorrhages and moderate atrophic emphysema. Gastro-intestinal tract shows no abnormalities except a small diverticulum in the œsophagus 8 mm. in diameter and 4 mm. deep, located in the anterior wall just below the bifurcation of the trachea; there are no evidences of adhesion of the external wall of the œsophagus to the surrounding tissues at this point. The large intestine contains fœces that are clay colored. The kidneys are enlarged, weighing 460 grams, are much stained with bile; cortex 8 mm. thick; capsule strips easily, occasionally tearing off

strips of cortex. In the spleen, which is embedded in adhesions, are many scars of healed anemic infarcts.

The heart weighs 360 grams, being slightly enlarged. The valves are all normal, and the size of the orifices is normal. There are numerous small subendocardial ecchymoses. Foramen ovale closed; interventricular septum normal. The beginning of the aorta is of normal diameter, and there is but slight sclerosis of the aorta, although the smaller arteries of the heart and throughout the body are considerably sclerosed. The wall of the

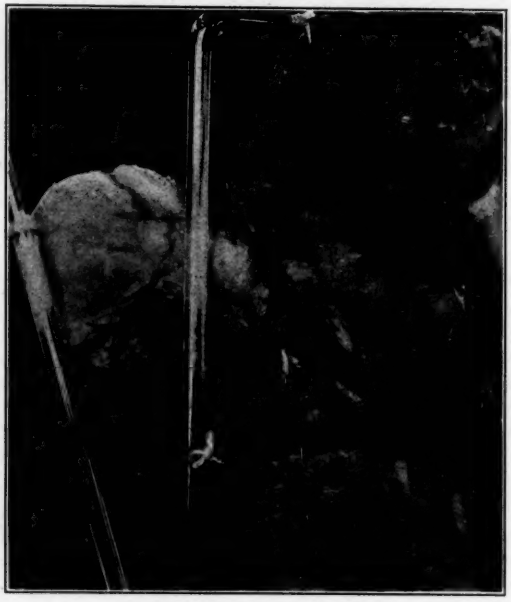


FIG. 1.—Patent ductus arteriosus. The black rod passes into the opening of the duct in the aorta, about which the sclerotic patches can be seen. The external surface of the duct is seen in its course to the segment of the pulmonary artery, the external surface of which is shown in the photograph. (Natural size.)

left ventricle is of normal thickness, while the right ventricle is slightly thickened. Pulmonary artery not sclerotic. At the normal location of the arterial ligament there is a duct-like communication between the aorta and the pulmonary artery, the patent ductus arteriosus (Fig. 1). The upper margin of the opening of the duct into the aorta is located about 5 mm. below the level of the lower margin of the left subclavian artery; at this point the lining of the aorta shows a slight transverse striation with apparently slight thickening of the subendothelial connective tissue. Here the internal

circumference of the aorta (hardened in alcohol) is 37 mm., while 2 cm. lower down the circumference is 45 mm. The length of the duct from the margin of the aortic opening to the pulmonary orifice is 16 mm. The aortic orifice is elliptical in shape, the greatest diameter is transverse of the aorta and measures 8 mm. The pulmonary orifice is bounded by a ring of thickened intima 5 mm. in diameter, from which projects a mound-like elevation, symmetrical, 1.5 to 2 mm. high, apparently formed by a proliferation of the margins of the orifice (Fig. 2). These folds are quite pliable, about as thick as the thickest part of a normal aortic valve. The opening of the duct is situated at the top of this mound, circular in outline,

FIG. 2.—The opening of the duct into the pulmonary artery, at the summit of a mound-like protrusion of the intima of the pulmonary artery. (Magnified three diameters.)

and measures 2 to 3 mm. in diameter. Although the aorta itself is nearly free from sclerosis, at the opening of the duct is a sclerotic patch 16 mm. long, 7 mm. broad, about 1 mm. thick, calcified into an elliptical plaque. This stretches across the lower margin of the aortic opening of the duct, transverse to the long axis of the aorta. The duct itself is in the form of a rigid, cylindrical tube, the external diameter averaging 10 mm. Its lumen shows an extremely sclerotic appearance, and the diameter of the cavity is quite uniform, about 6 mm., until the point of insertion of the duct into the pulmonary artery is reached, where it narrows down quite abruptly to the size of the pulmonary orifice. There are no evidences of thrombosis or of aneurysmal dilatation.

The anatomical diagnosis was as follows: General icterus; atrophy of the liver, with icteric necrosis and beginning atrophic cirrhosis; chronic parenchymatous nephritis; patent ductus arteriosus, with sclerosis of the ductus; atrophic pulmonary emphysema, with multiple ecchymoses in the lungs; fatty degeneration of the myocardium; healed infarcts in the spleen, with fibrous perisplenitis; multiple subcutaneous lipomas; diverticulum of the œsophagus; general arteriosclerosis.

To summarize, the condition of the patient's vessels had apparently nothing to do with his final illness, which was probably a catarrhal jaundice in a person with atrophic cirrhosis and parenchymatous nephritis. The patency of the ductus arteriosus had not led to any considerable effect upon the heart, except for a very slight thickening of the right ventricle; it is possible that the healed infarcts in the spleen were due to emboli coming from the ductus at some previous time, as there was no other apparent source for them. Clinically the patency of the duct had led to distinct physical findings, but does not seem to have given rise to noticeable symptoms.

Occurrence of Persistent Patency. Under normal conditions the ductus arteriosus ceases to be functionally patent, that is, to transmit blood from the pulmonary artery to the aorta, when the fully developed infant takes its first breaths. Complete anatomical closure, so that there is no lumen through which blood can find its way under any conditions, requires several days for its completion; in many perfectly normal babies the duct does not become impervious until from three to six weeks, although it usually closes much earlier, for Billard found only three in twenty still patent after eight days. Not rarely it happens that some part of the lumen remains open throughout life, and can be found in sections of the remnants of the duct, although complete impermeability exists at one or several points; not rarely a duct can be entered for some distance from one or the other end with a fine probe, and sometimes the probe may be forced completely through, but without the duct having been functionally patent. If we exclude these slight variations from the normal occlusion, and consider as instances of pathological persistence of patency only those cases in which the lumen of the duct has been free for the passage of blood during the life of the patient, the number of examples reported is small. It is to be emphasized that we are here considering only simple, primary persistence of the ductus arteriosus, for in nearly every form of congenital heart lesion and anomaly of the great vessels the ductus arteriosus remains patent, for reasons that will be discussed later; but in such cases the persistence of the duct is usually overshadowed by the other abnormalities, and the entire picture is quite different from the one under consideration.

In 1893 Vierordt stated that he could find but 26 authentic instances recorded in the literature, in which the existence of un-

complicated persistence of the ductus arteriosus was established by postmortem examination. These constituted but about 4 per cent. of all the recorded cases of congenital diseases of the heart and great vessels; thus the infrequency of this condition may be appreciated. Including cases not mentioned by Viero dt, and additional cases reported since 1898, I have found 15 more, making a total of but 41. There are about half a dozen other probable cases in which I have been able to obtain only such incomplete records that they have not been incorporated in the following table:

Age.	Total cases.	Male.	Female.
Newborn	5	1	2
1 to 3 months	6	1	1
4 to 12 months	1		
1 to 10 years	5	2	2
11 to 19 "	4	2	2
20 to 30 "	5	2	3
31 to 40 "	6	2	4
41 to 50 "	6	2	4
51 to 60 "	2		2
61 to 66 "	1		1
Total	41	12	21

If we consider only the cases in which the subject reached maturity, there are but 20, so that the condition present in the case reported herewith is indeed a rarity. However, it is certain that these figures give a very erroneous impression as to the frequency of persistent patency of the ductus arteriosus, for, in the first place, within the past few years there have appeared numerous reports of cases in which this diagnosis has been made clinically with a considerable degree of certainty, but without postmortem corroboration. Again, there is no doubt that very frequently the condition is overlooked by the examiner at the autopsy, for unless his attention has been called to the possible occurrence of such an anomaly it is easily missed in a careless or hasty examination; the usual manner of removing the heart is of itself disadvantageous, for the knife frequently severs the great vessels at or near the point at which the duct connects them.

Such cases, tabulated as above according to sex and to the age at which death occurred, show two interesting facts: (1) A decided preponderance of females, for which no explanation seems to have been offered; and (2) that the presence of this lesion is by no means imcompatible with a fair duration of life, although perhaps shortening it, since few of the subjects passed the fiftieth year. As in my own case, the patient may live an active and vigorous life although his duct is patent enough to cause marked physical findings, and death occurs from some unrelated affection.

THE NORMAL OCCLUSION AND OBLITERATION OF THE DUCTUS ARTERIOSUS. In order to understand the reasons for the occasional failure of the ductus arteriosus to undergo normal occlusion and involution, it is necessary to become familiar with the mechanism

by which this process is normally accomplished. There have been many hypotheses advanced to explain how and why the duct becomes spontaneously occluded, synchronously with the first successful efforts of the newborn babe to breathe. Among them may be mentioned the following: That the first expansion of the large bronchi by air compresses the duct (King); thrombosis and adhesion of the walls (Cruveilhier, and others); bending of the arch of the aorta by the increased pressure after birth (Magendie); tension and collapse through change of position of the thoracic viscera upon the beginning of respiration (Schantz,[10] Gérard); occlusion by fibrous growth in the intima (Thoma, Walkoff); active contraction by the muscular layers of the wall of the duct (Billard, Langer). I may mention particularly the suggestion of W. S. Forbes,[11] of Philadelphia (1880), that fibrous bands which pass over the duct are connected with the diaphragm, and upon its first descent are pulled down upon the duct and occlude it. However plausible some of these explanations may be, it is quite certain that not all of them apply to the normal process of closure of the duct. This is a physiological process taking place spontaneously and instantaneously in every newborn child, and therefore there must be some mechanism which can be relied upon always to perform this occlusion. Any explanation which involves connective tissue proliferation must be inadequate, for the duct is patent and carrying on its full function up to the moment of delivery, and then is at once occluded when the child begins to breathe; it is necessary to distinguish between the instantaneous *occlusion* of the duct and its subsequent *obliteration*. The theory of occlusion by thrombosis is also faulty, for ordinarily the occluded duct does not contain thrombi; even the ultimate obliteration is accomplished without the participation of thrombi, by means of the proliferation of the intimal connective tissue. All the hypotheses that are based upon the intermittent pressure from the respiratory act are obliged to assume the formation of thrombi to account for the permanence of the occlusion, since intermittent respiratory motions would only produce an intermittent form of occlusion, and hence these views must all be incorrect. What seems to be the proper explanation is the outcome of the investigations begun by Zuntz and carried on by Strassmann. Zuntz observed that at the aortic opening of the duct in full term animals there is present a thin crescentic fold along the upper margin, which is formed through the manner of insertion of the duct into the aorta; this insertion is at an extremely acute angle, about 33 degrees, so that the margin is thinned out to form the fold. This observation was extended by Strassmann to fœtuses of various species, including human, and investigated experimentally and microscopically. Zweifel corrobo-

[10] Pflüger's Archiv, 1889, xliv, 239.
[11] Amer. Jour. Med. Sci., 1880, lxxx, 88.

rated the correctness of these findings in the human fœtus, and the work has received further support from Roeder.[12]

In the human embryo the first signs of this fold begin to appear at about the sixth month, but it is not fully developed until the end of the eighth month, which possibly accounts for the failure of some apparently viable premature infants to live. The mechanism by which the fold at the aortic end of the duct accomplishes occlusion is as follows: In the fœtus *in utero* the pressure in the pulmonary artery is considerably greater than in the aorta, probably as high as a ratio of three to one; consequently blood flows through the duct (at this time larger than either of the two main divisions of the pulmonary artery) into the aorta. As soon as respiration begins, however, the dilatation of the lungs relieves the obstruction to the pulmonary vessels, more blood enters the left heart from the pulmonary veins, and consequently the pressure in the pulmonary artery falls and the aortic pressure rises, so that the relation of pressure becomes as much higher in favor of the aorta as it formerly was in favor of the pulmonary artery. As a result, blood ceases to pass from the pulmonary artery through the ductus arteriosus toward the aorta, and it cannot pass in the other direction because the pressure within the aorta forces the thin elongated margin against the opposite wall of the duct, blocking it completely. Strassmann tested the competency of this mechanism, and found that in the fully developed fœtus fluid injected into the pulmonary artery at pressures corresponding to the normal will pass readily through the duct into the aorta, but fluids injected into the aorta at normal pressure do not enter the pulmonary artery at all. If the pressure is considerably raised above the normal, the flap at the orifice of the duct becomes incompetent, either through its own stretching or through dilatation of the orifice, and extreme pressure may invert the flap into the duct.

It is in this way that the remarkable immediate occlusion of the duct at birth is accomplished. As long as the occlusion exists the duct has no function, and it at once begins to undergo changes of involution similar to those described by Thoma in the hypogastric arteries at the same period of life, or in ligated vessels between the ligature and the nearest branch. Apparently the contractility of the wall of the duct, although it is relatively poor in both elastic and muscular elements, is sufficient to prevent the entrance of blood from the pulmonary artery after the pressure in that vessel falls, for the finding of thrombi in the occluded duct is very exceptional. Different investigators disagree as to the point at which obliteration is first complete, some stating that the narrowed central portion is first completely occluded by the growth and contraction of the subintimal

[12] Gérard does not seem to have been able to confirm Strassmann's work, but his statements on this point are not extensive enough to assure one that his criticism is valuable.

connective tissue, while others maintain that obliteration takes place first at the ends of the duct. These differences concerning a simple matter of fact probably mean that there is no regularity in the place at which obliteration does first occur.

In the course of time fibrous tissue replaces the muscular and elastic tissues, so that these elements are scanty or wanting in the fibrous ligamentum arteriosus of the adult. Occasionally, however, remains of the original endothelial-lined canal can be found microscopically; and not infrequently the duct remains permeable to a fine probe for a few millimeters, most often at the pulmonary end. The length of the duct is, of course, modified by these changes; during the first two or three weeks it lengthens slightly, with the development of the thoracic organs, then gradually decreases a few millimeters in the child, but in the adult the ligamentum arteriosus is fully as long as the original duct, and often much longer. However, the length of the ligament is a very variable quantity, sometimes reaching 20 mm., and sometimes being practically absent, the aorta and pulmonary artery being then intimately adherent at this point.

Etiology of Persistent Patency. With the above facts in mind concerning the mechanism of normal occlusion of the ductus arteriosus, the conditions leading to persistent patency may be readily understood. Virchow considered these cases as of two classes: *primary patency*, in which occlusion of the duct had never occurred; and *secondary*, in which the duct reopened after having been more or less perfectly closed. The French writers consider as primary those cases in which the patency of the duct is the sole cardiovascular anomaly, and call the more common condition, in which there are other developmental defects in the heart and great vessels, secondary patency. It is possible to imagine that the duct may fail to become occluded, because of any one of the following causes:

1. When the insertion of the duct into the aorta forms a less acute angle than normal, the conditions necessary for the formation and functionation of the membranous fold of Zuntz and Strassmann at the aortic orifice of the duct are not present.

2. Local conditions, such as intra-uterine aortitis, congenital syphilis, or inadequate growth energy, may prevent the proper formation of the occlusive fold. Rickets has been present quite frequently in this condition.

3. Premature birth, as the fold is not completely developed until the end of the eighth month. Cases in which premature birth seems to have been the cause of subsequent patency have been reported by Bittorf,[13] whose patient was alive at twelve years, and by Rees[14] and Dresler.[15]

[13] Münch. med. Woch., 1903, 1, 1771.
[14] Trans. London Pathol. Society, 1848, i, 203.
[15] Jahrb. f. Kinderheilk., 1902, lvi, 705.

4. An abnormally large lumen or aortic orifice of the duct might render the fold inadequate.

5. Persistent high pressure in the pulmonary circulation, such as might be produced by respiratory difficulties in the newborn, or stenosis of the pulmonary arteries beyond the duct. Atelectasis is especially important in this connection, as also is acute bronchitis; and in a case of Roeder's a congenital goitre pressed upon the trachea.

6. Relatively low pressure in the aorta, as in congenital stenosis of the aorta or the aortic orifice of the left ventricle, in which case the duct is always patent and circulation is carried on as in the fœtus, by means of the pulmonary artery and the duct.

7. Excessive pressure in the aorta at or immediately after birth, by rendering the occlusive fold at the aortic end of the duct either relatively or absolutely incompetent.

Secondary patency, through reopening of an already occluded duct, is probably a relatively uncommon occurrence; yet it can be imagined that it might be produced in one of the following ways:

1. If shortly after birth, before obliterative changes have rendered the duct impermeable, the pulmonic blood pressure is unduly raised by respiratory troubles, such as bronchitis, atelectasis, pleural effusions, etc., blood may be forced through the duct toward the aorta under some considerable pressure; at this time the walls of the duct are considerably weakened by the degenerative changes that are associated with the obliterative process, so that they may readily become dilated and render the duct permanently patent. Roeder found that although the duct of the newly born fœtus will withstand a pressure of 80 mm. of mercury, which is above the normal pulmonic pressure of the fœtus, at 90. mm. aneurysmal dilatation begins, and at 110 to 120 mm. serious dilatation and damage to the media occurs. He believes that such pressures may be reached when the child is under the pressure of the expulsive forces of labor, and that if there is in the first few days any respiratory difficulty that causes blood to pass into the duct from the pulmonary artery, then dilatation and patency may become permanent, or, as in two of his cases, rupture may occur. It would seem probable that similar conditions may result in the thrombosed dilatation, aneurysms of the ductus arteriosus, which are observed not infrequently in young infants, and described by Gérard, Roeder, and others.

2. In cases of septic infection of the newborn, at the umbilicus or elsewhere, the obliterating duct is a favorable site for the formation of septic thrombi, which may prevent the normal obliterative processes and render the duct patent. Although Lancereaux and Rauchfuss believed that this is a common cause of patency, it is probable that such septic thrombosis is usually fatal, and therefore it can have little to do with persistence of the duct in the adult. Nevertheless, it is of interest to note that thrombosis of the ductus arteriosus, if present at all, is usually associated with septic processes.

3. It is quite possible that the fibrous obliteration of the ductus may be faulty even after proper temporary occlusion has occurred; as the child develops and blood pressure increases, the sclerotic ring at the aortic orifice of such an imperfectly occluded canal may dilate under the pressure of the blood, which then gradually forces open the old canal. Those cases in which the pulmonary end of the patent duct is more or less occluded by a perforated membrane, as in the cases described by Rokitansky, Wagener, and in my own case, may be explained as due to a gradual reopening of an imperfectly obliterated ductus until the closed pulmonic end has been forced out into the pulmonary artery and ruptured.

When we take into account all the ways in which pathological patency might possibly be produced, the fact that such patency is one of the most infrequent of pathological rarities is striking, and shows that under almost any condition the methods of closure are adequate. Probably the chief reserve defence, or "factor of safety," lies in the sclerotic obliteration of the duct, which may well be adequate to accomplish secondary occlusion even if the primary occlusion at the aortic orifice is defective. It is also possible, however, that failure of closure of the duct is a more common cause of unexpected death of newborn infants than is realized. Roeder suggests that infants with respiratory difficulties may frequently die because of reopening of the duct on account of the heightened pulmonary blood pressure, the mixing of the aortic and pulmonic currents that then occurs being incompatible with their existence.

If we look through the records of the cases that have been reported, it is apparent that, at least in infants, respiratory disturbances with the resulting rise in pulmonary blood pressure is a most important factor in all forms of ductus arteriosus defects, including not only patency, but also thrombosis, aneurysm, and rupture. In most of the adult patients, however, it has been impossible to ascribe a cause, probably because the infantile history is not known. Congenital syphilis does not seem to have been present, although it could be easily understood how it might influence the production of the anomaly. Many of the patients have been small, rachitic, and poorly developed, as if the developmental forces had been defective, but it is possible that the poor development may have been the result rather than the cause of the arterial anomaly. Heredity seems to play an important part in all forms of congenital heart disease, and it may be concerned in this particular form of circulatory malformation, as shown by the remarkable family studied by de la Camp.[16] In this family of six children all showed clinical evidence of having persistence of the ductus arteriosus; in the two oldest children, sisters, the manifestations were very pronounced and the lesions were causing circulatory embarrassment, while in the younger children the results had not

[16] Berl. klin. Woch., 1903, xl, 48.

become so evident. Although in none of these cases has anatomical proof of the diagnosis been secured, yet the clinical findings and the radiograms are sufficiently characteristic to make the diagnosis reasonably positive, at least in the more advanced cases. The parents of the children are both living and free from any signs of cardiac disturbance.

In a few cases there have been observed other developmental defects, suggesting that the arterial abnormality might be due to defective developmental forces. In one case hypospadias was present, in the case of Bittorf there was double inguinal hernia, and in my own case there was a short inguinal hernia. However, developmental defects have been observed so infrequently that they are probably of little significance. In a very considerable number of the cases a history of alcoholism in the father has been obtained, but it is rather difficult to establish a relation between this and the patency of the duct in the offspring.

Pathological Anatomy. Gérard classifies the conditions under which patency of the ductus arteriosus may occur as follows:

I. Simple, uncomplicated persistence of the ductus arteriosus.

II. Accompanied by malformations of the vessels, as follows:

(*A*) Permanence of orifices that are normally closed (before), at or after the moment of birth (arrest of development or malformations).

(*a*) Interventricular communication.

(*b*) Stenosis of the pulmonary artery either at its origin or in its course.

(*c*) Absence of the pulmonary artery.

(*d*) Anomalies in the aorta.

(*B*) Persistence of the foramen ovale.

(*C*) Multiple malformations, which affect all the anatomy and are incompatible with life.

III. Accompanied by malformations in more remote places (hypospadias, hernias, etc.) or by superimposed lesions (atheroma, acute aortitis).

In his classical article upon this subject Gerhardt divided the forms assumed by the duct itself into four groups, as follows:

1. Extreme shortening of the canal, so that it forms little more than the margin of the opening in both vessels.
2. Funnel shaped, with the wide end toward the aorta.
3. Cylindrical form, the duct being variable in length and width.
4. Aneurysmal dilatations of the canal.

Of these forms, by far the most common are the second and third types, in which there is a definite duct. Even in the cylindrical type the aortic orifice is generally larger than the pulmonary opening, and so there is more or less approximation to the funnel shape. My own case is an excellent example of this, the elliptical aortic orifice measuring 8 x 6 mm., the duct maintaining nearly the same diameter

until near the pulmonary opening, where it narrows abruptly. In all the cases in adults there is usually considerable sclerosis of the aorta just about the orifice of the duct, and also in the walls of the duct itself, which last feature is particularly marked in my own case. Presumably the sclerosis of the aorta depends upon the traction of the duct (Thoma); indeed, in normal individuals one of the first places in which a sclerotic patch appears in the aorta is usually just at the point of insertion of the arterial ligament. Thoma has suggested that some of these cases of funnel-shaped patent ducts are really examples of traction diverticula of the aorta, but this is probably incorrect, for, as Wagener points out, if the arterial ligament were exerting traction one would expect that the thin-walled pulmonary artery would give way rather than the more rigid aorta. In my case there was a small traction diverticulum of the œsophagus, and although no adherent tissue was demonstrable at the autopsy, it seems quite possible that the existence of the patent duct may have in some way caused this diverticulum.

The length of the patent duct in the adult cases is extremely variable, from practically nothing at all, in the first of Gerhardt's groups, to as much as 20 mm.; but generally it is shorter than the 16 mm. duct found present in my case. The diameter of the lumen is usually from 3 to 6 mm., but there are cases of dilatation to 1 cm. or even more; in two cases the duct permitted the entrance of the little finger, and Sanders (1860) described the lumen in his case as being as large as the descending aorta of the infant in which it was found.

On account of the eddying of conflicting currents at the point of entrance of the duct into the pulmonary artery, formation of thrombotic vegetations at this point is favored, and in cases of septic conditions or acute endarteritis, vegetations may form in and about the openings of a patent duct; such a case is illustrated in the article by Hochhaus.[17] Schlagenhaufer[18] has described an interesting case of acute aortic endocarditis produced by the influenza bacillus in a patient with a patent ductus arteriosus; vegetations were also present extending through the lumen of the duct and at both orifices, and from these pulmonary infarcts had been produced. I have already mentioned the fact that thrombosis may occur in the duct of newborn children with septic infections, especially of the umbilical cord; Rauchfuss observed this condition twelve times in 1400 autopsies on infants, in 2 of which the thrombi were purulent. Roeder's 2 cases, in which partial rupture of the duct was present in children aged, respectively, two and three days, are unique.

Two features that were present in some of the recorded cases have particular interest in connection with the pathogenesis of persistent patency, and they have been discussed and described particularly by Wagener, whose two cases presented these features. They are

[17] Deut. Arch. klin. Med., 1892, li, 1.

[18] Ztschr. f. Heilk, 1901, xxii, 10.

(1) a fold guarding the aortic end of the duct, and (2) the mound-like elevation upon which the pulmonic end opens. There can be little question that the fold across the aortic opening represents the membranous margin, described by Zuntz and Strassmann, which under normal conditions closes the entrance to the duct from the aorta. Normally this fold becomes fused with the surface of the duct against which it is forced by the aortic pressure, and loses its identity during the subsequent processes of sclerosis. In case it does not occlude the duct for any reason, it might well remain as a fold or ridge at the entrance to the duct; such a fold has been described in several cases.

The protrusion of the margins of the pulmonary orifice has been described in a number of cases, and is particularly well shown in my own case (Fig. 2). Rokitansky, indeed, says that the pulmonary orifice is always a small round ostium, which is surrounded by a wall and is located on the top of a papilla that seems to have been formed by the pushing out or evagination of the end of the duct. In Wagener's three cases there was a delicate membrane separating the lumen of the duct from the lumen of the pulmonary artery, into which this membrane protruded; in two of the cases the membrane occluded the duct entirely, and in one there were small perforations. The significance of this membrane or elevation at the pulmonary ostium of the duct is of interest, but it has not been determined. Gerhardt looked upon the membrane as the remains of an organized thrombus, but there is no good evidence to support this idea. It seems much more probable that it represents a tissue formed in the closure of the duct at the pulmonary end, which has later been forced into the pulmonary artery by the aortic pressure after the duct has been gradually dilated from the unclosed aortic end. Another possibility, also, is that the elevation represents the result of an inflammatory proliferation set up at the point where the aortic and pulmonic currents meet; in favor of this view are the histological findings in Wagener's cases, which were interpreted by this author as indicating a recently formed tissue. If the first manner of formation occurs, then we may have signs of patent ductus arteriosus appearing for the first time in adult life, through the opening up of an imperfectly occluded duct; on the other hand, if the proliferation reaction occurs at the pulmonary ostium, it is possible that the signs of patency may disappear because of spontaneous closure at this point, and there is at least one authentic instance of recovery from this condition (Balfour)[19] to support the latter hypothesis.

Aneurysmal dilatations have been observed chiefly in infants, usually associated with thrombosis. Gérard (1903) collected 17 cases from the literature, but he apparently examined only French

[19] "Clinical Lectures on Diseases of the Heart and Aorta," 1898, 3d edition, p. 243.

publications, for there have been many others published in other languages. In 1000 autopsies on children Thore (1850) found 8 instances of this condition, and Gérard found 2 in 100 infant cadavers, so that it is not an extremely unusual condition. The aneurysms undergo thrombotic occlusion early, being always found in this condition at autopsy, so that the reason they are not found in adults is probably that they are obliterated by connective tissue formation. The shape is usually spherical, and the size "from a coffee bean to a hazel-nut." The location is usually nearer the pulmonic than the aortic end. Since in all these cases the duct is occluded by thrombosis, they do not properly come into consideration as examples of patent ductus arteriosus. In one of Roeder's cases of rupture of the duct there was present a form of dissecting aneurysm. He thinks that high blood pressure during delivery may injure the duct and lead to aneurysm later if the duct remains patent, or, in other cases, that blood entering the weakened duct from the pulmonary artery after changes of involution have begun causes the aneurysmal dilatation. Since the duct is occluded by thrombosis, aneurysm is not incompatible with life, and is merely an autopsy finding. Some of the more dilated of the patent ducts found in adult cases may be looked upon as a form of aneurysm, but I have found no records of extensive, typical, aneurysmal dilatation, with its usual extension and pressure effects.

Results of Patency of the Ductus Arteriosus. These are very difficult to estimate, for the reports to be found in the literature give extremely varying pictures. In some cases a well-opened duct has been found in the body of an adult, without subjective signs or objective symptoms having been noticed during life, while, on the other hand, some writers believe that in infants failure of the duct to close is in many instances incompatible with life, the blood which enters the pulmonary artery under aortic pressure either interfering with the pulmonary circulation or else causing respiratory troubles. Obviously the results will depend largely upon the degree of patency that exists, and in such cases as those of Wagener, in which only minute perforations through an occluding membrane are present, it is certain that no ill effects could be produced. Very commonly, as in my case, the opening is large enough to lead to the presence of symptoms and signs of the lesion, yet without sufficient disturbance of the circulation resulting to interfere seriously with the health and activities of the patient. The great majority of the cases observed clinically and at autopsy are of this nature, and in very few of the latter cases has death been due to cardiac insufficiency. However, there are a few instances in which the communication between the pulmonic and the aortic circulation has been so free that serious disturbances have resulted. In some cases death has occurred in infancy with all the usual manifestations of a serious anomaly of the circulatory system; in a greater number

of cases the patient has suffered from childhood with palpitation, shortness of breath, and inability to perform severe or continued muscular exertion, these symptoms either continuing until the patient succumbs to some intercurrent affection, or, more rarely, dies from cardiac incompetence and its results. In the more typical cases cyanosis is either slight or entirely absent, for here the amount of blood going to the lungs is larger than normal, in contrast to the more common condition of pulmonary stenosis. Even in the simplest cases the heart is usually more or less affected. Almost always there is some degree of hypertrophy of the right ventricle, and frequently dilatation, because of the obstruction to the emptying of the right ventricle caused by the inrushing arterial current. As there is more blood passing through the pulmonary circuit than normal, the left auricle is usually dilated, and hypertrophy of the left ventricle may result from moving this increased volume of blood and in keeping up the aortic pressure. The pulmonary artery is dilated by the pressure, and in some cases sclerosis occurs. Von Schrötter has reported a case in which the dilated duct produced pressure upon the left recurrent laryngeal nerve, which passes about the aorta in immediate proximity to the duct. The foramen ovale is frequently found incompletely closed, but this is so common an occurrence, even in normal individuals, that it can only be considered when the foramen is not guarded, in the usual way, by the slit-like nature of the opening, but is functionally patent; but in this case we should be dealing with one of the more common conditions of multiple congenital circulatory anomalies, and not the simple or primary patency of the duct with which we are concerned.

Diagnosis. Although there are a few writers who, like Gérard, question the possibility of a positive clinical diagnosis of simple patency of the ductus arteriosus being made, yet there are certainly abundant clinical reports in which this diagnosis has been made with some degree of assurance, and in a few instances the antemortem diagnosis has been substantiated by postmortem demonstration. Quite a number of German clinicians have reported cases of patent ductus arteriosus based solely upon the clinical findings, and the supposedly characteristic features are brought out in their publications, among which may be mentioned, as among the more recent and instructive, those of Zinn,[19] de la Camp, Dresler, Arnheim,[20] Heichelheim,[21] Brettauer,[22] Schiffer,[23] Sidlauer[24] and Bittorf. Dalsjö,[25] in Sweden, has also described two interesting clinical cases

[19] Berl. klin. Woch., 1898, xxxv, 433 and 850.
[20] Ibid., 1903, xl, 616.
[21] Deut. med. Woch., 1903, xxix, 280 (Vereins Beilage).
[22] "Drei Fälle Persistens des Ductus Arteriosus Botalli," Zurich, 1905. W. Conradi-Maag.
[23] "Kasuistische Beiträge zur klinischen Diagnostik der Persistens des Ductus Arteriosus Botalli" (Giessen), Würzburg, 1903. H. Stürts.
[24] Arch. f. Kinderheilk., 1902, xxxiv, 331.
[25] Hygiea, Stockholm, 1904, iv, 225.

Perhaps the most positive in his opinion concerning the possibility of accurate diagnosis of this condition is G. A. Gibson,[26] of Edinburgh, who is fortified in this by the corroboration at postmortem of his diagnosis in one of his several clinical cases. Concerning the chief diagnostic characteristics, he makes the following statement: "Inspection may reveal no facts of importance; palpation yields the valuable sign of a long thrill following the apical impulse, and continuing beyond the recoil of the blood on the semilunar cusps, the shock of which may be felt during the thrill; percussion may negative the suspicion of any increase in cardiac dulness—in fact, it usually does so in uncomplicated cases; auscultation gives the second and the most invariable evidence of the lesion in the presence of a murmur which is pathognomonic. Beginning distinctly after the first sound, it accompanies the latter part of that sound, occupies the first pause, accompanies the second sound, which may be accentuated in the pulmonary area or may be doubled, and finally dies away during the long pause." Besides these features, the German clinical observers lay much stress upon a band-like area of dulness along the left margin of the sternum in the second and third intercostal spaces, produced by the dilatation of the pulmonary artery, and over which the murmur and thrill are most distinct; this feature was first emphasized by Gerhardt. The murmur is also quite distinct in the upper part of the left interscapular space (François-Franck). The dilatation of the pulmonary artery can be readily observed in radiograms, the shadow above the base of the heart pulsating synchronously with each ventricular systole; this feature is emphasized by all the more recent observers; generally the auricles and right ventricle are also enlarged. De la Camp insists upon the significance of the direction of the thrill, which can be palpated readily in the second and third left intercostal spaces when the opening is not too small; the thrill seems to travel from below out and to the left, upward, inward, and to the right; when this feature can be made out it is pathognomonic. Generally the murmur is transmitted into the carotids, and in many cases it is heard more loudly in the left than in the right; in several cases the left radial pulse has not been so strong as the right, although this is by no means characteristic. It should also be mentioned, in contradiction to Gibson's statement, that hypertrophy or dilatation of the heart to greater or less degree has been present in by far the larger number of all cases observed, whether clinically or at autopsy. In differentiation from the other congenital cardiac lesions, especially stenosis of the pulmonary artery, which is the most common, the absence or relatively slight amount of cyanosis is quite characteristic of patency of the ductus arteriosus. The sharp closure of the pulmonary valves, which is emphasized by several writers, is not always present,

[26] Med. Press and Circular, 1906, lxxxi, 572; Edinburgh Med. Jour., 1900, viii, n. s., 1.

possibly because when the pulmonary pressure becomes very considerably raised the cusps do not open wide enough to close sharply. In some cases there has been observed a form of pulsus paradoxus, four or five beats of full strength being followed by a similar number of weaker beats; this phenomenon is explained by François-Franck as due to a more rapid escape of blood from the aorta into the pulmonary artery during inspiration—which lowers the aortic pressure and weakens the pulse during this period.

From what can be learned in the latest writings it would seem that a positive diagnosis should be possible in typical cases, but there are many cases reported in which the clinical findings have been anything but typical. It must also be admitted that a small aneurysm of the aorta communicating with the pulmonary artery might produce the same effects, as shown by Brocq's[27] case, although it would probably appear suddenly and later in life than the congenital vascular abnormality. Particular emphasis is laid upon the importance of accurate diagnosis of this condition by the bold suggestion of Munro,[28] that it should be possible to close this abnormal channel by surgical intervention. He has convinced himself by operations upon the cadaver that such operative procedure is possible, the duct being reached by an incision dividing the sternum or cutting through the attachment of the ribs on the left side; its closure could be accomplished by ligature, or perhaps by crushing. Whether a patient with the poor condition of circulation and respiration which most of these patients exhibit in any case serious enough to warrant such a dangerous intervention could stand so severe an operation, is a question that would have to be decided for each individual case; it must also be considered whether the weakened circulatory apparatus would not be seriously embarrassed by the sudden stopping of a condition to which it has adapted itself to a greater or less degree. In any case, however, this suggestion is well worthy of consideration, and it does not seem so fantastic and impossible as it would have a few years ago, before successful operations upon the heart became a not uncommon occurrence.

Another reason for establishing an accurate diagnosis in these cases is that the prognosis is, as a general thing, better than in other congenital heart lesions. Cyanosis, congestion, and œdema are present only in exceptionally severe cases, in which the opening has been unusually large and when the patient has reached the last stages. The advanced age at which several of these patients have died and the absence or unimportance of the symptoms resulting from the lesions in most of the recorded cases are noticable features. It is also perfectly possible for healing to occur; this might either be brought about through thrombosis, or, as appears to be shown in my own case, a reactive proliferation at the margins of the opening

[27] Rev. de méd., 1885, v, 1046; 1886, vi, 786.

[28] Annals of Surgery, 1907, xlvi, 335.

of the duct into the pulmonary artery may cause occlusion of or at least an amelioration of the condition. Balfour has described what seems to be an instance of such spontaneous recovery. The patient was, in childhood, examined by James Begbie, who made a diagnosis of patent ductus arteriosus; ten years later the same diagnosis was made by Warburton Begbie, and ten years later by Balfour, the same diagnosis having also been made in the interim by Sanders. The patient was frequently observed from this time on by Balfour, and the condition gradually improved, until fifteen years after Balfour's first examination the lesion seemed to have become entirely healed.

LEUKANEMIA.

By Warren P. Elmer, M.D.,
INSTRUCTOR IN MEDICINE IN THE ST. LOUIS UNIVERSITY, ST. LOUIS.

The symptom complex first described by von Leube under the name of leukanemia has been a subject for discussion for several years; certain authors contend that it is only an atypical form of pseudoleukemia or leukemia, while others claim it to be a clinical entity, a true combination of leukemia and pernicious anemia. The following case resembles so closely those described by von Leube and others, that it seems worthy of discussion:

Mrs. J., aged twenty-five years, a Syrian, married, and a housewife, entered the Rebekah Hospital, April 22, 1907, complaining of weakness, dizziness, tinnitus aurium, extreme nervousness, and constipation. Her father, mother, and three sisters are in good health. There is no history of tuberculosis, insanity, or malignant disease in the family. The patient was rather delicate as a child; had measles when one year old, and smallpox when twelve years old. The menstrual history is without interest. She married at eighteen years of age; has three children, all in good health. She had a small abscess of the left breast after the birth of the first child; this healed without complications. The last child was born eleven months ago.

The patient came to America three years ago in perfect health, and remained so until March 10, 1907, when she had an attack of grip lasting about a week, at the end of which time she was able to attend to her household duties, although still somewhat weak. A week later a friend commented on her palor. About March 22 she began to notice increasing weakness and slight dyspnœa after climbing stairs or other exertion. On March 28 she was severely frightened by an insane person, and from that time on weakness developed rapidly. By April 10 weakness had become so marked

that she had difficulty in going about her work. Shortly after this she came to St. Louis and consulted a physician. Roaring noises in the head and weakness were at this time her only complaints. Weakness became more and more pronounced, sleep disturbed, and she began to be very nervous. She had never noticed any enlargement in the abdomen until this was pointed out by her physician just before entering the hospital. She eats and sleeps regularly, and uses no alcohol or drugs.

Physical Examination. April 25. Fairly well nourished woman; five feet two inches in height; weight, 110 pounds. (Normal weight, 120.) Temperature, 101°; pulse, 120, soft and bounding. The skin of head and face is pale and of a yellowish brown color, due in part to the natural swarthy complexion of her race. Many deep scars (smallpox) appear paler than the surrounding skin. The ears are very pale; there is no discharge; the hearing is acute. The eyes are rather dull, the conjunctivæ of a dirty yellowish tint.

The lips are very pale and dry. The mucous membrane of mouth is very pale; no ulcerations or abrasions. The tonsils are slightly enlarged and pale; no exudate. There are no enlarged glands in the neck or the axilla. Physical examination of the lungs shows no deviation from the normal. The apex impulse is plainly seen in the fifth intercostal space four inches from the midsternal line; it is rather quick and slapping in character. The absolute heart dulness begins at the fourth intercostal space and extends to the sixth rib in the parasternal line and four inches to the left of the midsternal line in the fifth intercostal space. At the apex the first sound of the heart is short and valvular in character; the second sound is rather loud and clear; at the aortic area both sounds are fairly clear and distinct; at the pulmonic area a blowing systolic murmur is heard and is transmitted in all directions for about two inches; the second sound is clear, but not accentuated. The liver dulness begins at the sixth rib in the parasternal line and extends two inches below the costal margin; at the midaxillary line it begins at the eighth rib and extends to the costal margin. The liver can be plainly felt two inches below the costal margin; hard, smooth, and not sensitive to pressure. The splenic dulness begins at the eighth rib in the midscapular line. The spleen extends from the margin of the ribs to the crest of the ilium and to the right as far as the navel; it is smooth, not sensitive to pressure. It causes prominence of the whole left abdomen. A notch can be felt at the level of the navel. There is slight tenderness in the right ovarian region. The genital organs are apparently normal, except for slight peroneal tear. There are no enlarged inguinal or popliteal glands, but there is very slight œdema at both ankles.

Urine (24-hour specimen): Quantity, 1050 c.c.; specific gravity 1014; no albumin or sugar; trace of albumoses. Sediment shows many epithelial cells, but no casts or leukocytes.

Feces: Hard; dark-brownish in color; very offensive odor; few particles of undigested food noticed. Microscopic examination reveals no animal parasites.

Blood examination (for details of the various counts see table): Remarkably low count of red cells; moderate increase of white cells, with slight relative increase of lymphocytes, and a small percentage of myelocytes; total absence of mast cells at all times. Especially noteworthy, is the remarkable number of young forms, both normoblasts and megaloblasts, often as many as five or six in each microscopic field. The megaloblastic forms show the greatest variation in size and shape. The nuclei are often of peculiar shape; multiple nuclei are not uncommon. They have a somewhat reticulated texture which stains rather poorly. Polychromatophilia is the rule with these forms. I am not prepared to state whether the lobulated or multinuclear forms are simply degeneration forms, or reversions to an early embryonic type, but the former explanation seems the more plausible.

On subsequent examinations the number of nucleated forms varied considerably in numbers, but the types illustrated could be found in almost every blood film examined from April 23 to the time of the patient's death.

Date.	Number red blood cells per c.mm.	Hemoglobin.	Number white blood cells per c.mm.	Small lymphocytes.	Large lymphocytes.	Polynuclear leukocytes.	Eosinophile mononuclear leukocytes.	Eosinophile polynuclear leukocytes.	Myelocytes.	Mast cells.	Number of normoblasts seen in counting 500 white cells.	Number of megoblasts seen in counting 500 white cells.
		%		%	%	%	%	%	%	%		
April 23	850,000	30	16,000	21	6.2	62.5	..	2.5	5.0	..	80	120
April 28	800,000	30	14,000	31	6.8	55.2	0.6	1.0	5.4	..	95	140
May 5	860,000	35	17,000	27	6.0	59.0	..	2.0	6.0	..	70	100
May 12	900,000	35	18,200	20	5.2	63.0	..	3.6	8.0	..	65	48
May 18	800,000	30	17,061	23	7.2	57.0	1.6	2.2	9.0	..	70	90
May 24	700,000	20	12,000	30	8.0	48.0	2.0	1.0	11.0	..	22	12

During the first week of the patient's stay in the hospital, weakness continued to be her most distressing symptom; the temperature ranged from 101° to 102.3°, the pulse from 120 to 130. The bowels were kept regular with 5-grain doses of phenolphthalein daily. Fowler's solution in 5-drop doses was given after meals, increasing the amount by 1 drop every other day. The urine and stools remained practically negative.

On April 28 the patient began to complain of slight pain in the

right ear, but examination proved negative. By the end of the first week she began to show slight improvement; the temperature ranged from 99° to 100.5°. The appetite improved somewhat; sleep was not so restless. The bowels, however, did not move so freely, and a soap enema was ordered, followed by a pill of aloin, belladonna, and strychnine to replace the phenolphthalein. Pain in the right ear became more severe. Examination revealed slight redness of the posterior portion of the external canal, and the drum head slightly cloudy but not bulging.

During the second week the patient's general condition improved steadily; the temperature ranged from 98.2° to 99.6°, the pulse from 110 to 120; the appetite remained fairly good, and the bowels regular. The patient slept a great deal. Roaring noises in the head were still annoying and pain in the ear had not improved. Examination showed increased redness of the external canal, and the drum head seemed to be slightly bulging. The spleen and liver showed no appreciable change. The heart action was very rapid, but regular; the hemic murmur in the pulmonic region persisted.

On May 8 the patient noticed during the previous night slight discharge from the right ear followed by considerable relief. Examination showed a small rent in the drum head, which was covered with thick yellow pus, from which cultures were made. The ear was irrigated with boric acid and adrenalin solution.

On May 15 the patient felt a little stronger; the temperature during the previous week reached 100° only once. The appetite was good; she sleeps a great deal. The discharge from ear had almost ceased. Cultures showed streptococcus and various other organisms (probably due to contamination).

On May 18 the patient complained of increasing weakness in the last few days; nervousness had also increased markedly; roaring noises in the head had become somewhat more annoying; temperature was not above 99°; the pulse, however, remained between 110 and 120. Physical examination showed little change from the day of admission. The urine still contained traces of albumoses. The stools remained negative except for evidences of intestinal indigestion. At this time the patient was taking 15 drops of Fowler's solution after meals. She refused to stay longer in the hospital.

On May 26 I was called to patient's house. She was very weak; pulse, 130; respiration, 36 and sighing in character. Physical examination showed no change in the liver or spleen. The heart dulness was slightly increased and the sounds were very weak. The murmur in the pulmonic area had almost disappeared.

On May 28 the patient died. An autopsy could not be obtained.

The general symptoms in this case resemble quite closely those of pernicious anemia, while the physical signs might be taken as almost positive evidence of splenic or splenomyelogenous leukemia.

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The blood picture, however, is most unusual; while in the main it resembles pernicious anemia and myelogenous leukemia, the number of young forms is much greater than is found in either leukemia or pernicious anemia. One must consider the relatively small number of cells present, making the number of nucleated forms relatively more numerous. The otitis media may have had some bearing on the case, as many authors have noted streptococcic infections complicating leukemias, or followed by a leukemic blood-picture. The late appearance and the fact that the existing blood-picture was not appreciably modified by it would, I think, indicate that it was only incidental and had no important bearing on the progress of the disease.

The case described by von Leube[1] was that of a boy, aged ten years, who was brought to the hospital unconscious. Three days previous his teacher had noticed that he was very pale, and two days later he began to complain of pain in the neck and nose bleed and became unconscious. Physical examination showed the temperature 101°; the pupils equal; no stiffness in the neck; the skin and mucous membranes very pale; liver and spleen greatly enlarged; the heart dulness increased, but no murmurs. Blood examination: red cells, 256,000; white cells, 10,500; hemoglobin, 10 per cent.; nucleated red cells very numerous. Differential count showed polynuclear luekocytes, 40 per cent.; small lymphocytes, 40 per cent.; myelocytes, 15 per cent.; mononuclears, 2 per cent. Death occurred on the fourth day after entering the hospital. Postmortem examination revealed greatly enlarged spleen and liver, the latter showing amyloid changes, but not siderosis; no enlarged lymph glands. The bone marrow of the femur in its lower one-third was red, in the upper two-thirds fatty. Microscopic examination of the spleen showed many small areas resembling abscesses, but cultures were negative. The case was believed to be one of grave infection of unknown origin.

Weber[2] describes a case in a man, aged fifty years, who came under his care complaining of weakness, anorexia, and tinnitus aurium. Physical examination showed the temperature 100°, the pulse 88, the radial artery sclerotic; and the skin very pale and yellowish. The liver reached from the eighth rib to navel, the spleen from the eighth rib to the crest of the ilium and to the right as far as the navel. There was slight œdema of ankles. Blood examination: red cells, 1,800,000; white cells, 5000; hemoglobin, 25 per cent. Differential count showed polynuclear leukocytes, 37.5 per cent.; small lymphocytes, 49.4 per cent.; large lymphocytes, 10 per cent.; myelocytes, 3 per cent. Four megaloblasts and three normoblasts were seen in counting four hundred leukocytes. Poikilocytosis was pronounced. The patient died three weeks later. Postmortem examination

[1] Deut. Klin., 1902, Nr. 42.

[2] Brit. Med. Jour., June 18, 1904.

revealed greatly enlarged spleen and liver, no enlarged lymph glands, red metaplasia of the bone marrow, and hypertrophic hemolymph glands. Microscopically, bone marrow was found to be almost all fat, but it contained many nucleated red cells, some of which showed partially divided nuclei and multiple nuclei. The liver contained many myelocytes and nucleated red cells infiltrated between cords of liver cells; the spleen also contained many nucleated red cells.

Kirchensteiner's[3] case was a woman, aged forty-one years, coming under observation for weakness, headache, some pain in the bones, shortness of breath, and palpitation of the heart. She was well up to three weeks before entering hospital. Physical examination showed the skin pale, with somewhat yellowish tint; slightly enlarged heart dulness; the liver reached to level of navel; the spleen from eighth rib to ilium and to the right as far as the navel. The red blood cells were 885,000, the white blood cells 6700, the hemoglobin 18 per cent. A differential count showed polynuclear leukocytes, 77 per cent.; lymphocytes, 10 per cent.; myelocytes, 8 per cent.; large mononuclears, 4 per cent.; eosinophiles, 1 per cent.; normoblasts, 570 to the cubic millimeter; no typical megaloblsts. Five days later the red blood cells were 250,000, the white blood cells 53,000, the hemoglobin 16 per cent. A differential count showed much the same relationship as above, except that polynuclear leukocytes reached 78 per cent., while lymphocytes decreased to 5 per cent. The autopsy revealed nothing of importance.

Mosse,[4] reports the case of a woman, aged fifty years, who had been well up to about six months before coming under his care. She had become weak and pale, short of breath, and complained of loss of appetite. She had rather profused menstruation six months previously, and since then has not menstruated. Physical examination showed a pale, waxy skin; the spleen reached from the eighth rib to the anterior superior spine of the ilium and to the right as far as the navel; it was slightly sensitive to pressure. The liver was somewhat enlarged. Blood examination: red cells, 2,665,000; leukocytes, 30,870; hemoglobin, 50 per cent.; megaloblasts and normoblasts, very numerous. Differential count showed polynuclear leukocytes, 44 per cent.; mast cells, 5 per cent.; eosinophiles, 13 per cent.; myelocytes, 18 per cent.; eosinophilic myelocytes, 1.3 per cent.; lymphocytes, 3 per cent.; myeloblasts, 7.5 per cent. At the time this paper was written patient was still alive.

Teeter[5] reports a case with recovery in a child, aged ten years, in which megaloblasts and normoblasts were greatly increased, and accompanied by moderate enlargement of the liver and spleen.

[3] Münch. med. Woch., 1905, Nr. 21.
[4] Berl. klin. Woch., 1907, Nr. 49.
[5] Jour. Amer. Med. Assoc., February 16, 1907.

The number of white cells, 132,800, would tend to place this case at least on the border line.

The case reported by Luce,[6] Bushnell and Hall,[7] Morawitz,[8] and a few others do not seem to me typical. Preis[9] reports a case under the title of atypical leukemia, which, had the finding been described more in detail, might have belonged in this series.

The question as to whether or not leukanemia should be considered a clinical entity is worthy of further discussion. The cases here abstracted correspond rather closely, both as regards physical examination and blood findings, while several other cases, reported as leukanemia or atypical leukemia, gradually shade off toward the more typical leukemias, especially the acute myelogenous. The theory of Pappenhein[10] deserves consideration: he believes that leukanemia should not be considered a separate disease, but a combination of pseudoleukemia and myelocytosis; that the same cause which brings about any anemia may act as well in a case of pseudoleukemia; and that the same cause, in certain susceptible individuals, may bring about both conditions.

It is a matter of common knowledge that myelogenous leukemia is associated with considerable anemia and that the blood findings almost always show normoblasts and occasionally megaloblasts. Several authors have observed leukemic changes in the blood following infections, and this at times is accompanied by enlarged spleen.

Hunter[11] has demonstrated more or less clearly an infectious origin for pernicious anemia, and undoubtedly some cases with a clinical picture of pernicious anemia are due to infections. Certain toxemias also may be considered as a cause of pernicious anemia and of leukemia. The temperature at least in the cases reported as leukanemia is suggestive of an infection. Reasoning from this rather imperfect basis, it seems logical to suppose that while leukanemia has a very definite clinical and hematological picture, it is not a separate disease, but the result of some unknown infection which in certain individuals might cause an anemia, in others a leukemia, and in still a third class, who are especially susceptible, a clinical picture which combines the two. Further careful observations of cases of this character should throw considerable light on the etiology of both the leukemias and pernicious anemia.

I wish to express my gratitude to Dr. G. C. Crandall, through whose kindness I studied the case herewith reported.

[6] Deut. Arch. f. klin. Med., Band lxxvii.
[7] Edin. Med. Jour., 1906, p. 329.
[8] Deut. Arch. f. klin. Med., Band lxxxviii.
[9] Ztschr. f. klin. Med., 1905, lvii.
[10] Ztschr. f. klin. Med., 1904, lii.
[11] Brit. Med. Jour., November 9, 1907.

THE PATHOLOGICAL ANATOMY OF BRONCHIAL ASTHMA.

By A. G. Ellis, M.D.,

CORINNA BORDEN KEEN RESEARCH FELLOW OF THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

(From the Pathologico-Anatomical Institute (Prosector, Dr. Ludwig Pick) and the First Medical Department (Prof. Dr. Stadelmann) of the Städtisches Krankenhaus in Friedrichshain, Berlin, Germany.)

Owing partly to lack of definite knowledge regarding the pathological anatomy of bronchial asthma, various theories have been advanced concerning its nature. The explanations given by different clinicians may be placed in three groups:

1. *Spasm of the Diaphragm.* First propounded by Wintrich, this theory has been supported by a number of later writers. Riegel and Edinger[1] conclude that spasm of the diaphragm, more than spasm of bronchial muscles, plays an important part in asthmatic attacks. Their opinion was based on experimental studies, and possibly is entitled to more than usual attention, because they had fully expected to prove exactly the opposite. More recent writers are in general not favorably inclined toward this view.

2. *Spasm of the Bronchial Muscles.* This view of Biermer's[2] still has many adherents, some holding it to be the principal feature, others at least a part of the asthmatic phenomenon. Riegel and Edinger state that their own and other experiments indicate with certainty that the smooth muscle fibers of bronchi contract upon irritation of the vagi; that this is the cause of asthma, however, is not proved. Their view that this is less important than spasm of the diaphragm has been mentioned. Lazarus,[3] from experiments on rabbits, concludes that both bronchospasm and asthmatic catarrh are necessary to produce bronchial asthma. Talma[4] regards the affection as primarily due to spasm of the muscles of the respiratory tract. These muscles are, to a certain extent, under control of the will, or can be brought under control, hence his method of treating the disease by respiratory gymnastics. Aufrecht[5] convinced himself that the musculature of the finer bronchi consists (as in animals) of a stout layer of circular and a much weaker layer of longitudinal fibers, the effect of the contraction of which is evident. Nevertheless, he does not admit that asthma must be regarded as a consequence of bronchial muscle cramp, since the affection may be due to catarrh of the finer bronchi.

[1] Ztschr. f. klin. Med., 1882, v, p. 413.
[2] Volkmann's Samml. klin. Vorträge, 1870, Nr. 3.
[3] Deut. med. Woch., 1891, Nr. 27, p. 852, and Nr. 36, p. 1057.
[4] Berl. klin. Woch., 1898, Nr. 52, p. 1141.
[5] Deut. Archiv f. klin. Med., 1900, Band lxvii, p. 586.

Fraenkel[6] says the theory of bronchial muscle cramp explains, for the most part, the phenomena of the asthmatic attack, and experimental physiological investigations regarding contractility of the bronchi give this some support. These investigations, however, give too little consideration to undoubted changes in the bronchial mucous membrane. Elsewhere, in discussing the mechanism of spiral formation, he assigns a necessary function to bronchial spasm, stating that, in addition to the tenacity of the bronchial secretion, at least an indirect part is taken by such contraction. The latter, narrowing the bronchial lumen, has to do with consistence of the mucus, and interferes with the passage of air. When this spasm fails, as in ordinary asthma, tenacious sputum alone is not formed into spirals.

Pieniazek[7] regards the view that attacks of bronchial asthma are due to cramp of small bronchi as not tenable; much more probably are they due to swelling of the mucous membrane in the smaller bronchi. Grossmann[8] says the power of contractility of the bronchial muscles can be no longer denied. This is, however, by no means strong enough in itself to produce a grave respiratory disurbance. Experimentally it is not possible to produce contractions of the bronchi without at the same time causing circulatory changes in the pulmonary vessels. Clinically, doubtless these two conditions always run parallel. On the other hand, changes in the pulmonary circulation can, experimentally as well as clinically, appear without contraction of the muscles. Upon the degree and rapidity of onset and disappearance of this circulatory change depend also the degree and acuity of the respiratory disturbance.

3. *Bronchial Catarrh.* That this condition forms a large, if not indeed the principal, part of the pathology of bronchial asthma is believed by many observers, some of whom have been quoted in the preceding paragraphs. Fraenkel says that mere catarrh of the finer air passages is to be rejected as the only cause of asthma, because it furnishes no basis for the suddenness of the attacks. It is doubtful if in all cases catarrh goes before spasm of the muscles, although it appears plausible that spasm of muscles might easily follow when bronchioles are partly closed by swelling of the mucosa and the presence of tenacious content. Pieniazek, in upholding this theory, states that swelling of the mucous membrane can occur very quickly, as is seen in cases of œdema of the uvula, in urticaria, etc. Retardation of expiration is better explained by this than by muscle cramp. Pathologically he regards asthma as standing between pure œdema and acute catarrh. To paralysis of the small bronchial veins he assigns the swelling of the mucous membrane.

[6] Spezielle Pathologie u. Therapie der Lungenkrankheiten, 1904.
[7] Wien. klin. Woch., 1905, Nr. 46, p. 1201.
[8] Ztschr. f. klin. Med., 1907, Band lxii, p. 179.

Aufrecht believes that asthmatic attacks of a day and longer are better explained by assuming the presence of catarrh.

Whatever the changes in the bronchi, or the diaphragm, may be, they apparently are the result of a primary disturbance in the nervous system. Hoffmann[9] states that by asthma we understand a neurosis in the domain of the respiratory nerves, which shows itself by attacks of dyspnœa, with characteristic secretion and distention of the lungs; the affection is, perhaps, a pathological change in the respiratory centre of the medulla. Fraenkel's view is that the asthmatic patient has to charge for the greater part, probably even exclusively, the peculiar condition of his nervous system as the source of his disease. In the majority of instances this condition is a hypersusceptibility of that portion of the nervous system which is in direct relation to the respiratory tract. In a series of cases the responsible focus is a circumscribed area which, through gradual pathological changes, becomes an irritation point, from which attacks develop, as in many forms of nasal asthma. In a second type there is increased irritability of the collective mucous surface from the nose to the bronchi, and in a third there possibly exists a similar condition in the bulbar respiratory centre. Finally, in a minority of cases, the remainder of the nervous system may be at fault, as in asthma, which is one of the phenomena of general neurasthenia. With right, therefore, he says, asthma may be designated a reflex neurosis.

Materials from which to determine the pathology of asthma are principally two—the sputum ejected by persons suffering from the disease, and the lungs of those who die during an attack. The former, largely a clinical question, about which a great deal has been written, I shall later discuss briefly in connection with certain points relating to lesions found in the lungs. As regards the latter, I have found in literature the reports of but seven cases in which histological studies were made of the lungs of asthmatic subjects who died during an attack of that disease. The findings in these may be thus briefly summarized:

Case I (von Leyden[10]).—Female, aged forty years. From childhood had almost daily attacks of asthma. Died in an attack during cyanosis, dyspnœa, and stertor. At autopsy a high grade vesicular emphysema of both lungs was found. The bronchi were not dilated; the mucosa was reddened, but not otherwise abnormal. Microscopically some of the alveoli were dilated; others were not. They were filled with granular material in which was embedded a moderate number of large cells. In the smaller bronchi was a similar material tightly adherent to the walls and narrowing the lumina; at one point this substance formed a plug-like mass that

[9] Nothnagel, Spec. Path. u. Ther., Band xiii.
[10] Deut. Militärärztl. Ztschr., 1886, Heft ii.

completely occluded the bronchus. Neither fibrin nor Charcot-Leyden crystals were found in this mucous material occupying the bronchi. The walls of the bronchi were not essentially changed.

CASE II (Berkart[11]).—Female, aged thirty-seven years, who had suffered from attacks of asthma during a period of fourteen years, finally dying in a state of dyspnœa and general congestion. Autopsy showed hypertrophy and dilatation of the heart and emphysema of the lungs. In the right primary bronchus was a dark brown clot-like plug, almost closing the lumen; a similar mass was in a branch of the left bronchus. Many of the smaller bronchi were not only dilated, but were also partly occluded by exudate. Microscopically the epithelium was absent from the wall of the right bronchus over the area in contact with the plug, and also from the smaller bronchi, where there was an ostensible fibrinous exudate. The medium sized bronchi were more or less nearly filled by detritus-like masses, in which were fragments of Charcot-Leyden crystals. The brownish clot in the right bronchus consisted chiefly of degenerated epithelium in connection with spirals. Among the epithelium were cylindrical types which showed change into thread-like forms of variable length, some of these appearing as whip-like projections on fairly well preserved cells. Similar long-drawn-out cells had also been found in the sputum. A part of the emphysematous pulmonary alveoli contained fibrinous exudate.

CASE III (Schmidt[12]).—Female, aged forty-nine years, who had developed asthma in addition to a medullary carcinoma of one lung. Patient died during a severe exacerbation of an attack lasting a week. Section of the lungs showed that the peripheral somewhat dilated bronchi of the upper lobe of each were surrounded by grayish pigmented, strongly compressed tissue here and there beset with caseous foci. They contained spiral-formed mucous threads, which were unusually adherent to the walls, but could by forceps be drawn out in masses many centimeters long. Microscopic examination showed that in the majority of the small dilated bronchi the epithelium was well preserved. By the application of various staining methods (Weigert's thionin, triacid) it was clearly demonstrated that the content was, for the greater part, mucus, with a few cellular elements and Curschmann's spirals. The spirals diminished toward the periphery, and only in certain places could a turned appearance of the content in the respiratory bronchioles be noted. Nowhere in the considerably dilated alveoli could a spiral be found. The mucosa and submucosa were infiltrated by round cells. For the greater part the lumina were entirely filled with a homogeneous material in which were embedded, in addition to spirals, various types of cells. These included alveolar epithe-

[11] On Bronchial Asthma, 1889, 2d edit.
[12] Ztschr. f. klin. Med., 1892, Band xx, p. 476.

lium, a moderate number of leukocytes with lobed nuclei (but none with eosinophile granules), homogeneous, round, oval, or spindle cells, with neither nuclei nor granules, and epithelial cells, sometimes in masses. The content of the ducts of the mucous glands showed no especial consistence or winding, though the glands were in strong secretion. As typical central threads were found also in the smaller glandless bronchi, it was evident that they were a secretory product of neither the mucous glands nor their ducts. Surrounding the mucus-filled bronchi were areas of considerable alveolar dilatation; these alveoli contained a slight amount of granular material or were entirely filled with a substance resembling that in the bronchi and shown by thionin and triacid to be mucus. The bronchi containing no mucus were empty or contained cells the larger number of which were polynuclear leukocytes. Surrounding the latter bronchi were bronchopneumonic areas; that is, the septa were infiltrated, the alveoli were emphysematous, and in them were many alveolar epithelial cells and leukocytes without intercellular material.

Case IV (Fraenkel[13]).—A man aged sixty-three years, who, during his last year, had many attacks of asthma. At autopsy both lungs were found widely expanded, meeting in the middle line. In the left primary bronchus was a large quantity of thin mucous fluid. The lung was largely air-containing, and on the border were many cherry-sized emphysematous vesicles. The bronchial mucous membrane was strongly reddened, the lumina were dilated, and in part filled with tough masses which could be pulled out in the form of thready clots. The right lung possessed extensive adhesions, and the cut surfaces showed marked œdema. The bronchi were widened and contained material similar to that in the left. The walls of the larger bronchi were thickened and at points showed scars and lime deposits. The bronchial glands were large and pigmented.

In stained sections from the bronchial clots typical large spirals were not seen, but instead a large number of thready, in part wound, formations, staining blue, and not entirely homogeneous, but slightly granular in appearance (fibrin?). Other similarly formed clots consisted of cylindrical epithelium, in part close together, in part irregularly placed, in part palisade-like, as before desquamation. In a few was a suggestion of winding. Eosinophiles were not perceptible.

Microscopic examination of the tissue showed a high-grade desquamative bronchial catarrh. The cylindrical epithelium was detached and filled the lumina, being in part in serpentine form, in part as distinct bands around a central axis. These cell accumulations were in some places so great as to fill the bronchial

[13] Ztschr. f. klin. Med., 1898, Band xxxv, p. 559.

lumen. The vessels of the mucous membrane were dilated, the peribronchial tissues infiltrated with small cells. In consequence the denuded mucous membrane was at points elevated, and the bronchial wall appeared not inconsiderably thickened. The lung was in part normal, in part emphysematous, with, at points, increase of interstitial and interalveolar tissues. In many places alveoli were filled with blood, and in others, in the vicinity of dilated bronchi, the lumina and walls were so filled with lymph cells as almost to arouse the impression of beginning suppuration. At other points the lungs showed atelectasis, partly due to dilatation of bronchi, partly to increase of connective tissue.

CASE V (Fraenkel[14]).—A woman, aged forty-eight years, who, at various times, suffered from asthma, during the last period being under observation for more than a year. Attacks occurred almost daily. The tenacious sputum contained numerous coagula, with Curschmann's spirals and asthma crystals therein. The last typical attack occurred thirty-six hours before death. In spite of this the majority of middle-sized and small bronchi were found at autopsy to be filled with exquisite screw-shaped coagula, some many centimeters in length. Sections of the lung were stained by a modification of the Biondi-Heidenhain method, and showed, as did Schmidt's, that the bronchial effusion was entirely of mucus. In many of the dilated small bronchi were spiral figures whose centres stained the same as the mucous cell content of the epithelium lining the tube, while the mesh-like spaces of the periphery contained numerous eosinophiles.

The genesis of the coagula in the small bronchi of 0.15 to 0.3 mm. lumen could be distinctly followed. First was a considerable increase in the ciliated cells of the epithelial covering, of which isolated cells throughout were very much longer than the normal, the transverse diameter being correspondingly diminished. Some cells were 20 microns high. The nuclei were still normal. Mucus protruded from the cell bodies and into the lumina of the bronchioles or passed over directly into spirals. At many points, in some over the entire circumference, numerous large epithelial cells were loose and so far from the wall that three or four lay behind each other. These free cells were drawn out, in part large spindle-formed, and showed on the end toward the bronchial wall whip- or awl-like thin projections, which lost themselves between the cells that were not so greatly changed and were still attached to the wall. Other changes in the bronchi were hyperemia of the mucous membrane, with small blood extravasations, and the specially striking appearance of numerous heaps of closely placed leukocytes in the thickened walls of the bronchioles. These cells were largely eosinophiles, of which the majority were mononuclear, similar to

[14] Deut. med. Woch., 1900, Nr. 17, p. 269.

those already mentioned as in the lumina of the bronchi. In the immediate vicinity of the eosinophiles, and in part surrounded by them, were groups of well-formed Charcot-Leyden crystals.

CASE VI (Jezierski[15]).—A man aged sixty-three years, whose father also died of asthma. Had first attack in 1900, followed by others in 1903 and 1904. Died of right-sided pneumonia in two days while under treatment for asthma. At autopsy the right lung was large and heavy, the middle and upper lobes liver-like in consistence. The left lung was small, light, slightly pigmented; the bronchi were dilated, their mucosa red. The cut surfaces of the right upper lobe were dark red and covered with foamy fluid; of the middle lobe, grayish yellow to red, and with protruding granules. Isolated, many-branched fibrin plugs were in the small bronchi. Material saved for microscopic study included medium and smaller bronchi of the left lung, pieces of the right lung, diaphragm, and both phrenic and vagi nerves.

Microscopically the bronchioles showed in the lumina closely crowded cell masses in addition to well-preserved cells, chiefly ciliated epithelium, which singly or in rows had desquamated or remained hanging to the basement membrane by long thin stalks; among them were also round, non-ciliated epithelium, numerous leukocytes, lymphocytes, erythrocytes, and eosinophiles, all embedded in a ground substance which was shown to be mucus. Fibrin was not demonstrated. At the basement membrane the epithelium was well preserved, though between the elements were round cells. The latter were also numerous in the walls and peribronchial tissues, some diffusely placed, some in heaps, arranged in part like lymph nodes. The quantity of elastic tissue was unusual, far exceeding that in the lungs of other individuals of the same age, and of arteriosclerotic persons, with which they were compared. Also unusual was the presence in the bronchial walls of an abundance of small bloodvessels. On transverse section of the bronchi these vessels appeared closely crowded together, forming, as it were, a palisade-like wall around the tunica propria. In some of the vessels were isolated fibrin threads. In the perivascular lymph spaces were numerous cocci, mainly diplococci; these were also found sparsely in the lumina of the bronchioles. The peribronchial tissues were likewise infiltrated by round and blood cells. Study of the diaphragm and the neck muscles showed rarification and fatty infiltration of the former; otherwise nothing abnormal. The vagi and small nerves of the neck were intact. The phrenic nerves showed, by Marchi and Flemming safranin staining methods, some changes, a part of the fibers being tinged blackish brown, or swollen or notched in a bead-like manner. The right lung showed a typical pneumonic condition.

[15] Deut. Archiv f. klin. Med., 1905, Band lxxxv, p. 342.

CASE VII (Jezierski).—Female, aged forty-six years, who had attacks of asthma for twelve years, death from dyspnœa occurring during an attack. In each pleura was, approximately, 200 c.c. of bloody serum. The left lung was markedly emphysematous, but on section showed a good blood content. On pressure there flowed from some bronchi small, worm-shaped, quite consistent mucous masses. The right lung on section showed somewhat smaller worm-shaped structures, but otherwise was like the left. Small pieces of these clots examined fresh showed an enormous quantity of epithelium, mostly ciliated, with long clear nuclei and heavy cilia. The majority were striking because of their unusual narrowness and length, especially the end threads, which often reached one-third the diameter of the field ($\frac{1}{12}$ oil immersion), as already described by Berkart and Fraenkel. In addition was cuboidal epithelium from the deeper layers, numerous round cells, isolated red cells, and masses of detritus. In sections of the clots the nuclear structure and narrowness of the thread-formed epithelial cells did not show so clearly; there appeared here numerous eosinophiles, round and polygonal epithelium, many with two nuclei, pale, barely tingible cell remains, and, as ground substance, mucus.

The bronchi, on transverse and longitudinal section, showed mostly intact and undamaged epithelium. Only in isolated places was it detached or broken through by masses of round cells. These penetrated between the epithelial cells as rows, passed into the basement membrane, and infiltrated widely the bronchial walls and peribronchial tissues, either diffusely or in isolated masses. In part they were small, mononuclear, with scanty protoplasm, but the majority were larger, with dark, indented nuclei and abundant protoplasm; they were most numerous in the vicinity of vessels. The smaller the bronchus the more numerous were the cells, often so many in the lumen and surrounding tissues that the bronchial structure was not clear. The elastic tissue was in this case not increased, neither was there the new vessel formation as in the first. The pulmonary parenchyma was intact.

Through the courtesy of Professor Dr. Stadelmann, Director of the Department of Internal Diseases, and of Dr. Pick, Prosector of the Friedrichshain Hospital, I am enabled to add to this list another case. To both these gentlemen, and especially to Dr. Pick, for his kind supervision of my work, I hereby express my warmest appreciation and thanks.

CASE VIII.—O. S., a coachman, aged twenty-seven years, was admitted to the hospital April 2, 1907, and died on the following day. Owing to the severe dyspnœa of the patient, his previous history could not be obtained from him, but later was ascertained through the courtesy of Dr. Carl Bruck, of Berlin, who had treated him during the previous year for attacks of bronchial asthma. The man had also exhibited tachycardia, but neither Dr. Bruck

nor a consultant from the University of Berlin could discover a lesion referable to the heart. Neither considered the attacks of asthma as being in any way related to the heart, regarding them, therefore, as pure bronchial asthma. At the time of admission the face and extremities of the patient were strongly cyanotic; œdema was not present. There was severe expiratory dyspnœa, with coughing expiration. The asthmatic attack continued almost unbroken through the day and night and until evening of the following day, when the symptoms abated and the patient slept. At 9 P.M. he suddenly collapsed and died. The clinical diagnosis was bronchial asthma and heart failure.

At autopsy the anatomical diagnosis was: Hypertrophy of left ventricle; dilatation of right ventricle; pulmonary emphysema; purulent bronchitis; exudative bronchiolitis. The body was that of a strongly built man. With exception of the face, cyanosis was marked. The lungs were distended, entirely covering the pericardium. The heart was of good color, the wall of left ventricle 1.5 cm. thick, the right ventricle somewhat dilated, and the muscle flabby. The valves were smooth. The right lung was slightly adherent to the thoracic wall, greatly inflated, soft, and easily indented. On section the organ was strongly red in color and not of excessive air content. By pressure on the lower lobe pus could be expressed from the bronchi. The bronchial mucous membrane was red in color. On the cut surfaces of the lung could be seen numerous shiny, often greenish colored mucous plugs, which protruded from the finest bronchial branches. There were also fine, worm-like, mucous clots 2 to 3 cm. long, corresponding to the small mucous-filled bronchi. The larger masses of mucus were yellowish green in color, those in the finer bronchi more whitish and clear in appearance. The left lung was not adherent to the thoracic wall, but otherwise was like the right.

The material studied histologically consisted of several blocks of tissue from various parts of each lobe of both lungs; after fixation by Zenker's fluid, it was hardened in alcohol, and finally embedded either in paraffin or celloidin. Numerous sections from each were stained by hematoxylin, with the addition of eosin or Van Gieson, Schmidt's and Fraenkel's modifications of the Biondi-Heidenhain method, Weigert's elastica, Gram-Weigert, and thionin.

Microscopically, the lumina of the majority of the smaller bronchi possessing a diameter of from 0.13 to 0.16 mm. are partly or entirely filled with material which, in different places, varies slightly in its constituents. In general there is a ground substance, slightly granular or almost homogeneous in appearance, in which, at points, are embedded a few cells. Staining by Biondi-Heidenhain and thionin shows in every instance this substance to be mucus. In sections from some of the blocks are bronchi in which this mucus is arranged in distinct spiral form. In these formations the central

portion is quite dense and homogeneous, staining deeply and uniformly; the peripheral parts are less dense, and react less intensely to stains. The latter portions contain a variable number of cells, which become more numerous as the wall of the bronchus is approached. A few of these cells are mononuclear, and appear to be the remains of partially degenerated epithelial cells, *but desquamated epithelium is in these bronchi exceedingly scanty, those cells*

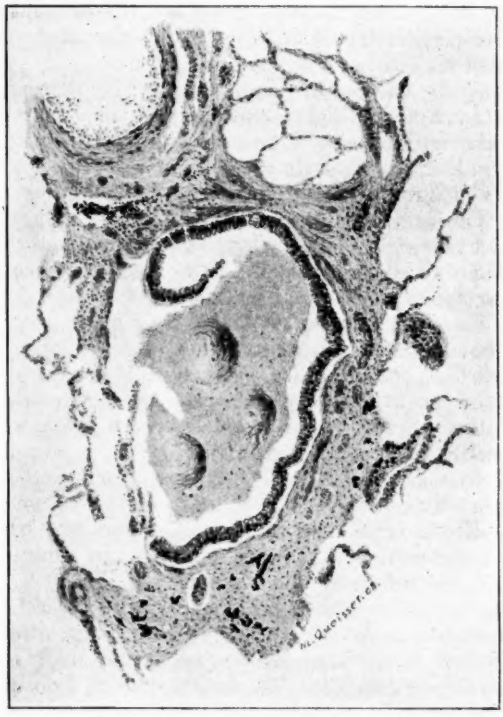

FIG. 1.—Bronchus of 0.3 mm. lumen containing three spirals in cross-section. The epithelium is intact, except on the left where the wall has been mechanically torn. (Leitz ocular 1, objective 3.)

in general being still attached to the wall. Instead of being elongated, they are either of normal appearance or are even flattened by the exudate, the average height being 7 microns. The majority of the cells in the lumen, and they are numerous in none of the bronchi of this size, are polynuclear leukocytes. Occasionally is seen an eosinophile, but those cells are nowhere numerous, and none has been observed directly within a spiral; they are polynuclear in type.

In bronchi of larger size, from 0.2 to 0.45 mm. in diameter, with, at points, well-preserved epithelium, are also spiral formations (Fig. 1), or isolated central "threads" or a granular material, in which are, at points, fairly numerous cylindrical epithelial cells; *the latter show no elongation*, measuring 13 microns in height. Some of these are irregularly placed, while others still bear the same relation to each other as before desquamation, appearing as palisade-like masses placed at some little distance from the basement membrane, and forming a boundary to the central mucous content of the tube; the space between these cells and the bronchial wall is in many instances entirely clear. In the central parts are isolated epithelial cells and enormous numbers of polynuclear leukocytes, eosinophiles being few or absent. In some of these bronchi the entire lumen is filled by a mass of polynuclear leukocytes, granular material between them being very scanty. At certain points the

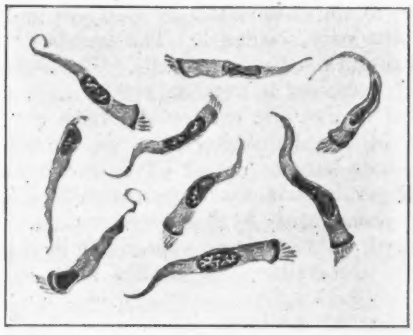

FIG. 2.—Elongated desquamated epithelial cells from the bronchial mucosa. (Leitz ocular 1, objective 7.)

epithelial lining has disappeared and the content of the lumen merges gradually, almost imperceptibly, with the greatly infiltrated bronchial wall. At one point hemorrhage has occurred into the bronchial lumen from an eroded vessel. In such of these bronchi as contain considerable quantities of mucus, this material is arranged in the form of definite striæ running in the longitudinal axis of the lumen, the contained leukocytes also showing a similar linear arrangement. In many places the polynuclear cells are all thus placed in rows in which the individual cells are nearly or quite in contact.

In other still larger bronchi, with lumina of 0.8 mm., are small or greater quantities of mucus and desquamated epithelial cells. Some of the latter are distinctly elongated (see Fig. 2), reaching a length of 35 microns, *but these are only isolated cells, scattered here and there among a much greater number normal in length.* In only

a few instances do these cells appear similar to those pictured by Fraenkel, and then are in no way equal in quantity or regularity to those found in his case. They lack entirely a definite relation to the mucus contained in these bronchi. In some bronchi of this size eosinophiles are fairly numerous. Charcot-Leyden crystals have been seen in none of the specimens.

The walls of the bronchi, especially the smaller, are markedly infiltrated by leukocytes. Those immediately beneath the basement membrane are, in all instances, almost exclusively polynuclear in type; external to the muscle coat mononuclears, mainly large, with vesicular nuclei, are in evidence, but even here the polynuclears are in many places numerous. These cells in some locations extend to a few of the surrounding alveoli, giving the suggestion of small foci of peribronchial pneumonia. Among the cells in the bronchial walls are also eosinophiles, all polynuclear in type. In some bronchi they are scanty, and in others, especially the middle-sized, very numerous; in one of the latter are thirty-six in one field of the Leitz $\frac{1}{12}$ oil immersion, ocular 1. The vessels of the bronchial walls are dilated and filled with red cells. The leukocytes in them are considerably increased in number, and in many vessels are distinctly marginal in location; eosinophiles have not been seen in these vessels. Minute hemorrhages in the bronchial walls are occasionally found, but are not at all a prominent feature. In some of the larger bronchi the basement membrane and tunica propria show pronounced hyaline degeneration. The muscles appear unchanged and there is no appreciable increase in the connective tissue of the walls. The elastica likewise is apparently normal.

The parenchyma of the lungs shows some changes. In many parts the alveoli are distended, with, in some instances, rupture of the walls and consequent formation of variously sized emphysematous spaces. The alveolar capillaries are quite uniformly engorged. Alveoli bordering the bronchi and containing mucus and leukocytes have been mentioned, but at some points not in demonstrable relation to bronchi are groups of several alveoli each that are partly or almost entirely filled by mucus, in which are embedded numerous leukocytes (90 per cent. polynuclear), desquamated alveolar epithelium, and red blood cells. This material is slightly more granular than is that in the bronchi, and also lacks the striation of the latter. In alveoli in various parts of the sections, some containing but little exudate, are polynuclear eosinophiles in numbers varying usually from one to four to the alveolus, but in one instance an alveolus contains eleven of those cells.

The larger bloodvessels of the lung show in general no striking change, except all contain more than the usual amount of blood. Many contain small quantities of fibrin, a few even small coagula of fibrin and leukocytes. In sections from one block, however, is

a medium-sized vessel containing a plug of leukocytes, essentially all polynuclear in type. This vessel extends in one section half the width of the field of a Leitz objective 3, ocular 1, and is throughout almost solidly filled by leukocytes, containing only at points a few red cells. Isolated small arteries show splitting and fragmentation of the inner elastic lamina in part of their circumference; one vessel has attached to this portion of its wall a small thrombus.

In comparison with previously reported findings, the prominent features of this case are: (1) The presence of mucus in the finer bronchi, with the formation therein of spirals. For the formation of these bodies the coöperation of cells appears not to have been essential, since desquamation of epithelium is here slight or entirely lacking, and leukocytes are present only in small numbers, and chiefly at the periphery of the spirals. The cylindrical epithelial cells of these bronchi are not elongated, but, on the contrary, are, at points, flattened by the exudate. (2) In bronchi of larger size the epithelium is partly or entirely desquamated, and polynuclear leukocytes appear in large numbers, both of these elements being added to the mucus or spirals, as the case may be. (3) In some of the middle-sized bronchi a few of the cylindrical epithelial cells show elongation, but this is in no instance a regular or prominent feature.

Collectively these reports of autopsy findings show that *the pathological anatomy of bronchial asthma is not the same in all cases*, though in some points they quite closely correspond. Later writers agree that the essential process is in the finer bronchi, and not the alveoli, though v. Leyden[16] expressed the belief that lymph-like fluid passes into the alveoli, and in part into the smaller bronchi, and there coagulates. Riehl's cases, mentioned later, are apparently an exception to this statement regarding location of the process, but since his view, well founded clinically, lacks the support of histological study, it cannot be accepted as negating actual tissue findings. The later cases also agree in the bronchial content being mucus instead of fibrin. Desquamation of bronchial epithelium, though present in most cases, varies considerably as regards location and extent. Fraenkel regards the desquamation of epithelium in the smaller bronchi as one of the two essential features of asthmatic catarrh, and his cases lend weight to that view. On the contrary, in the case of Schmidt, Jezierski's second case, and in mine, the epithelium in the finer bronchi was in general well preserved. This point is of special interest in its bearing upon the part taken by these cells in the formation of spirals, Fraenkel believing that the central threads, not improbably the "free" threads, and naturally a part of the centre of the spirals, are formed from the elongated ciliated epithelial cells.

[16] Deut. med. Woch., 1891, Nr. 37, p. 1085.

TABLE GIVING SUMMARY OF THE FINDINGS IN THE EIGHT REPORTED CASES OF BRONCHIAL ASTHMA COMING TO AUTOPSY.

Case.	Lungs macroscopically.	Bronchial lumina microscopically.	Bronchial content.	Bronchial epithelium.	Bronchial wall.	Pulmonary alveoli.
I. Female, 40 years. v. Leyden (1886).	High grade vesicular emphysema. Bronchi not dilated; mucosa reddened, but not essentially changed.	In smaller bronchi narrowed by content; at one point plug-like filling.	Granular material in which moderate number of large cells are embedded. Mucus. no fibrin; no crystals.	....	Not essentially changed.	Some alveoli dilated, some not; some contain granular material and large cells.
II. Female, 37 years. Berkart (1889).	In right primary bronchus and branch of left, dark brown plugs. Many small broncni dilated and partly occluded by exudate.	Medium sized more or less occluded.	Ostensible fibrinous exudate in smaller. Detritus-like masses with fragments of Charcot's crystals in medium. Degenerated epithelium and spirals in large.	Desquamated where the exudate is in contact.	.....	Some of dilated alveoli contain fibrinous exudate.
III. Female, 49 years. Schmidt (1892).	Peripheral bronchi somewhat dilated, and contain long, spiral, mucous threads, quite tightly adherent to wall.	Small for greater part entirely occluded.	Homogeneous mass, in which are alveolar and bronchial epithelium, polynuclear leukocytes, round, oval, or spindle cells and spirals. Mucus. No eosinophile granules.	Well-preserved in majority of small dilated bronchi; at points absent.	Mucosa and submucosa infiltrated with round cells.	Alveoli in some places contain material same as in bronchi (mucus). Bronchopneumonic areas around some bronchi.
IV. Male, 63 years. Fraenkel (1898).	High-grade emphysema. In left primary bronchus large quantity of thin mucous fluid. Bronchi dilated; mucosa reddened.	In medium and smaller, plug-like occlusion by elongated cylindric epithelium.	Partly wound threads. Granular material (fibrin?) Cylindric epithelium. No eosinophiles.	High-grade desquamation.	At points thickened. Vessels dilated. Peribronchial tissues infiltrated by round cells.	Some alveoli contain blood, some lymph cells. Emphysema in parts, atelectasis in others.
V. Female, 48 years. Fraenkel (1900).	Middle-sized and smaller bronchi filled with long, screw-shaped coagula.	Majority of small and middle-sized occluded.	Mucus. Spirals. Desquamated epithelium. Numerous eosinophiles.	Pronounced elongation and desquamation.	Hyperemia and small hemorrhages. Numerous leukocytes, largely eosinophiles; near them Charcot-Leyden crystals.	

VI. Male, 63 years. Jezierski (1905).	Right, pneumonia (hepatized). In left, small bronchi dilated, mucosa reddened.	Bronchioles filled with exudate.	Mucus. Ciliated epithelium, leuko- and lymphocytes, erythrocytes and eosinophiles.	Superficial desquamated, lower layers well preserved.	Numerous round cells in wall and peribronchial tissues. Elastica increased. Many new bloodvessels. Numerous diplococci in perivascular lymph spaces.	
VII. Female, 46 years. Jezierski (1905).	Left, markedly emphysematous. Worm-shaped mucous masses from small bronchi of both lungs by pressure.	Smaller large lyocc-luded by round cells.	In clots examined separate from tissue are numerous elongated cylindric epithelial cells and eosinophiles. Mucus.	Only in isolated places detached.	Enormous number of round cells, mainly large in size.	Remained intact.
VIII. Male, 27 years. Ellis (1908).	Emphysematous. Fluid (pus) in larger bronchi. Mucous plugs in small bronchi. Bronchial mucosa reddened.	Most of smaller partly or entirely occluded by exudate.	Mucus. Cylindric epithelium in middle and larger. Polynuclear leukocytes. Few polynuclear eosinophiles. Spirals. No crysta'a.	Extensive desquamation of cylindrical cells in middle and larger, not in finer bronchi.	Infiltrated by leukocytes, mostly polynuclear. Many eosinophiles. Hyperemia. Hyaline degeneration of basement membrane in large bronchi. Elastica not increased.	Vesicular emphysema. Exudate in small areas. Eosinophiles in alveoli.

These elongated cells had been noticed by Berkart, who suggested the possibility of their forming spirals; Fraenkel stated that his case is the first in which this formation has actually been demonstrated. *That this is not the method in all instances, however, is shown very clearly in my experiments with spirals formed from mucus in small bronchi in which epithelial desquamation had not occurred.*

In other respects, as regards the number and type of leukocytes, the presence of Charcot-Leyden crystals and eosinophiles, elongation of epithelial cells, and changes in the component parts of the bronchial wall, the cases differ widely. In the accompanying table I have stated briefly the findings in each of these respects, and the points of resemblance and difference may there be noted. Jezierski, from a comparison of his cases, tentatively concludes that equally typical symptoms of bronchial asthma can be drawn out through at least two different originating conditions, and that, therefore, there is not a uniform etiology of those symptoms. Fraenkel also states that comparison of his two cases shows that, during asthmatic attacks, the pathological anatomy is not in every case the same. He, however, regards as a common band uniting them all the extensive epithelial desquamation in the bronchioles, the other essential feature being the secretion of unusually tenacious mucus. I have already shown that the former cannot be regarded as a common and essential feature, since it is not present in all cases.

The findings in the lungs, therefore, explain the sputum of bronchial asthma only to a very limited degree. This is not surprising in view of the fact that the term "characteristic," so often applied to the material expectorated by persons suffering from this disease, is a misnomer. Viscid mucus is possibly the most constant constituent, and in it may be embedded epithelial cells, leukocytes of various types, eosinophile cells, Charcot-Leyden crystals, and spirals. When all these are present a quite striking picture is produced, but one or more of these elements may be lacking, and, what is of much greater importance, almost identical material has been expectorated by persons suffering from other affections. Kaufmann[17] states that spirals are found in the sputum of other diseases of the lungs, as croupous pneumonia and bronchopneumonia, fibrinous bronchitis, and pulmonary œdema. He has repeatedly found them in the tough mucus behind stenoses of the bronchi, due to anthracotic bronchial lymph nodes or to tumors, primary or secondary, of the bronchial wall. Each of the other elements mentioned has also been found in the sputum in connection with diseases other than bronchial asthma.

With the possible exception of Fraenkel's one case, the reported tissue studies furnish cumulative evidence that spirals are formed from mucus. Schmidt says no doubt has existed about the mucous

[17] Lehrbuch der spez. Path. Anatomie, 1907, Auf. 4, p. 204.

nature of the outer spiral windings, but there has about the central thread. He concludes that at least the typical Curschmann spirals possess also a centre of mucus, and therefore have nothing to do with fibrin. He, however, found fibrin masses in the sputum of six or eight cases of asthma, but always sharply separated from the accompanying spirals. Even these findings are so at variance with other reports that later writers justly regard them as strongly suggestive of cases of fibrinous bronchitis. Schmidt's statement that the best method of demonstrating spirals in sections of sputum is the use of Weigert's fibrin stain also permits criticism of his findings, even though he decolorizes the sections until only a pale blue shimmer remains. I am quite convinced that errors in differentiating fibrin and mucus arise from the use of this stain, whatever the details of the technique may be. This possibility I proved to my own satisfaction with material from the case reported. Staining with a weak solution of thionin and examining the section under water, as recommended by Schmorl, I find one of the best methods of demonstrating mucus in tissues. To avoid the use of alcohol entirely, Liebermeister,[18] before removing the paraffin, stains sections for five minutes with a weak solution of thionin, removes the paraffin with xylol, and mounts in balsam. This method gives fairly satisfactory results.

Schmidt's modification of the Biondi-Ehrlich-Heidenhain stain for tissue sections, as given by Fraenkel, is as follows: A stock solution is made by dissolving 1 gram of the mixture in 30 c.c. of distilled water and allowing this to stand for some time. The staining fluid is then made by taking of the stock solution 2 c.c., distilled water 40 c.c., 0.5 per cent. acid fuchsin solution 3 c.c., and 0.2 per cent. acetic acid solution 4 drops. In this the sections are placed for twenty-four hours, rapidly washed with 90 per cent. alcohol, dehydrated in absolute alcohol, cleared in xylol, and mounted in balsam. Fraenkel, after washing with 90 per cent. alcohol, stains one-half minute with 1 per cent. iodine-green in 2 per cent. carbol water, differentiates in 90 per cent. alcohol until neither red nor green color appears, and completes the mounting as already given. Mucus is stained green, and, at least in my sections containing fibrin in the bloodvessels, fibrin a purplish violet. Eosinophiles are well stained.

Predtetschensky[19] examines sputum by placing it on a black surface and isolating the characteristic flecks. These are placed on a slide and a cover-glass pressed down upon them. When spirals are found microscopically, the cover is slid off and the slide dried in air. The after-steps are: (1) Fix in methyl alcohol three to five minutes; (2) dry in air; (3) stain thirty to fifty minutes with (*a*)

[18] Deut. Archiv f. klin. Med., 1904, Band lxxx, p. 551.
[19] Ztschr. f. klin. Med., 1906, Band lix, p. 29.

30 drops of Reuter's stain (Grubler), or (*b*) 10 drops Giemsa in 10 c.c. distilled water; (4) wash with distilled water; (5) cover and seal with vaselin. These preparations last for several days. From his studies of sputum he concludes that the chief constituent of spirals is eosinophiles, the mucus serving only as binding material for those cells. He describes three types of spiral structures: (1) Broad spirals without central threads; (2) typical spirals with central threads; (3) isolated central threads. Only the last mentioned, in addition to rudimentary spirals, show a simple structure, and consist solely of thin mucin threads. He says one cannot hold Curschmann's spirals as specific for bronchial asthma, but only as a bronchial secretion, out of which, during attacks, the spirals form, the latter consisting of mucus and enormous quantities of eosinophile cells. None of the eight reported cases furnishes confirmation of this view.

In this discussion of the site of the lesion and of the spirals in bronchial asthma, the observations of Riehl[20] deserve a place. He reports sputum studies from four cases—two in males, two in females—in which the spirals differed considerably from those in ordinary cases, and which suggest an unusual location of the disease process, although not necessarily a difference in the process itself. In the sputum of each patient were "giant" spirals ranging from 6 to 24 cm. in length, and in some instances attaining a breadth of 3 to 3.5 cm. Microscopically no spirals of the ordinary size were found. Charcot-Leyden crystals were found in none of the specimens. Riehl can account for the large spirals only by assuming that they were formed in bronchi of the first order, instead of in the smaller tubes. The clinical course supported this assumption, there being in general a lack of considerable dyspnœa and of physical phenomena in the air passages. There was severe dyspnœa while the spirals were being expectorated, as was not surprising in the presence of masses capable of obstructing large bronchi. The patients were usually ill several days before cough and expectoration began. Riehl regards the cases as illustrating a variant of bronchial asthma, in which only isolated larger bronchial branches were affected—an "isolated" rather than "diffuse" asthma. None of the cases coming to autopsy has been of this type.

Schmidt is correct in stating that *it is impossible from anatomical findings alone to construct a picture of the mode of origin of spirals.* According to his view the power that produces the central threads from mucous masses must have its application within the bronchial lumen, and, corresponding to the gradual formation of spirals, its action cannot be narrowed to any fixed point. He believes this producing power can be no other than the rotary movement of the air which is forced through the tough mucus and which acts upon

[20] Münch. med. Woch., 1906, Nr. 46, p. 2240, and Nr. 47, p. 2302.

that material during its entire passage from the finer to the larger bronchi.

As a final statement regarding the nature of spirals is to be noted the opinion of Kaufmann. He states that for the production of spirals, which consist of mucus, there is requisite the presence in the bronchi of a scanty, tough, mucous secretion which, by violent respiratory efforts, by the associated pressure and the convulsive movements, possibly also by contraction of the bronchi themselves, is formed, and turned and driven forward. In this process the central part of the mucous string becomes so dense that it appears as a shiny, homogeneous thread (which, however, is no peculiar structure in itself), surrounded by the looser spiral mucous mantel. He states without comment that Schmidt regards this mucus as a special secretion of the finest bronchi, which possess no mucous glands, and that Fraenkel holds it to be the cylindrical epithelial cells of the finer bronchi which have undergone mucous degeneration.

The origin and significance of the eosinophile cells and the crystals often found in the sputum and the pulmonary tissues in cases of bronchial asthma is a widely discussed and still unsettled question. Both are found in other affections, hence neither is specific for asthma. Literature on the former subject is so extensive and so connected with the subject of eosinophilia in general that it would lead too far afield to consider it here *in extenso*. It will not be amiss however, to refer to a few of the earlier and some of the more recent opinions regarding the nature of eosinophiles, especially in the respiratory tract, and their connection if any, with Charcot-Leyden crystals. Their possible etiological relation to Curschmann's spirals has already been mentioned.

Lewy[21] concludes that these crystals, as well as the spirals, are only a consequence of the desquamating catarrh in the bronchi, and are not specific for a special clinical disease picture. Later[22] he states there is a relation between eosinophile cells and the crystals, but considers it impossible to say just what this relation is. Weiss[23] discusses a moot question—the local formation of eosinophiles. He found those cells in the sputum from cases of chronic bronchitis with acute exacerbation and of pulmonary tuberculosis, in addition to that of bronchial asthma. In the last two he states specifically there was no increase of eosinophiles in the blood. He believes they do not come from that source, and that they are undoubtedly locally formed. That they are an etiological factor in bronchial asthma he regards as improbable. Aronson and Philip[24] found that in the sputum of a nine-year-old asthmatic patient nearly two-thirds of the whole number of cells were eosinophiles. A noteworthy point was that a large number of these cells were mononuclear, a type

[21] Ztschr. f. klin. Med., 1885, Band ix, p. 522.
[22] Ibid., 1900, Band lx, p. 59.
[23] Wien. med. Presse, 1891, Nrs. 41-44.
[24] Deut. med. Woch., 1892, Nr. 3, p. 48.

seldom found in the blood. They, however, found that the eosinophiles in this patient's blood ranged from 15 to 17 per cent. of all the leukocytes. Teichmuller[25] found eosinophile cells in the entire respiratory tract of guinea-pigs, cows, sheep, swine, horses, and rabbits. He believes one may well regard the lungs and bronchi as local forming places for these cells. Later[26] he describes cases of "eosinophile bronchitis," specially characterized by the great number of eosinophile cells in the sputum.

Fuchs[27] concludes that eosinophile cells have no one method of origin. They can arise from neutrophile granules, and also, by phagocytosis, from metamorphosed red cells. Their origin is restricted to no one place, and they may arise in all tissues and in all organs. The eosinophiles of sputum probably originate in the respiratory tract. They are of no differential diagnostic value in bronchial asthma, as they may appear in all diseases of the respiratory tract unaccompanied by fever. Stschastnyi[28] reaches similar conclusions regarding eosinophiles being formed through the phagocytosis by mesenchyma cells of fragments of hemolyzed erythrocytes. Consequently, eosinophiles can be formed wherever hemolytic and phagocytic processes are active; usually the principal sites are the bone-marrow, lymph nodes, spleen, and lungs. The appearance of eosinophiles in asthma, he believes, is explained by the observation of an unusual collection of those cells in the region of the bronchi after the injection into the blood of hemolytic serum. In asthma, with the observed vasomotor disturbances and hyperemia of the bronchial mucous membrane, there are furnished conditions favorable to the destruction of red cells and their ingestion by mesenchyma cells.

Pröscher[29] says we must accept that with the greatest probability the eosinophiles in bronchial asthma are locally formed. Though for some years believed to occur, the direct transformation from tissue cells to eosinophiles had not hitherto been observed. He details experiments made upon guinea-pigs which he regards as furnishing positive proof of such transformation, and hence of the local formation of eosinophiles, thus giving a sound experimental basis to previous theories. He employed intraperitoneal injections of non-absorbable teniotoxin, this producing a rich eosinophile exudate, in which could be clearly traced the transformation from eosinophilic granulated endothelial cells to mononuclear eosinophilic leukocytes. Pröscher holds that eosinophile granules are identical with hemoglobin. Mosny and Harvier[30] report what they believe to be the first recorded case of local meningeal eosinophilia, and

[25] Deut. Archiv f. klin. Med., 1898, Band lx, p. 576.
[26] Ibid., lxiii, p. 444.
[27] Ibid., 1899, Band lxiii, p. 427.
[28] Beiträge z. path. Anat. u. allg. Path., 1905, Band xxxviii, p. 456.
[29] Folia Hematologica, 1905, Band ii, p 543.
[30] Arch. de méd. exp. et d'anat. path., 1907, No. 3, p. 273.

regard it as proving incontestably that eosinophiles originate from lymphocytes. The patient was a man aged twenty-six years, suffering from syphilitic meningo-encephalitis. In the meningeal exudate they traced all forms of cells between the lymphocyte, or original cell, and the polynuclear eosinophile. The patient recovered; hence their studies were limited to the cerebrospinal fluid and the blood. The latter never contained more than 1 per cent. of eosinophiles. Brown[31] considers it probable that in trichinosis eosinophiles arise from degenerated muscle cells.

In opposition to these opinions regarding the local formation of eosinophiles, a number of writers favor the view that those cells found in bronchial asthma and in other affections arise in the hematopoietic organs, or at least are not locally formed. Müller[32] regards the Charcot-Leyden crystals as the primary occurrence, the eosinophiles as a result. The former are the crystallization product of a substance which possesses a positive chemiotaxis for eosinophiles. Wolff[33] studied the blood of a patient during and between attacks of bronchitis and asthma. The eosinophiles ranged from 6 to 14 per cent., and were little changed during the attacks. In another case of asthma, 7 per cent. of the cells in the sputum were eosinophiles, while those cells in the blood varied between 15 and 39 per cent. Heineke and Deutschmann[34] report a case believed to be unique. A patient who had had bronchial asthma for four years showed, at the beginning of attacks, a diminution of the eosinophiles in the blood, from 2.1 per cent. to 0.4 or 0.6 per cent., and then later, corresponding to the appearance of those cells in the sputum, an increase up to 10 per cent. They believe it impossible that the enormous number of eosinophile cells in the sputum could have come from a source other than the blood; only this supposition can explain to them the rapid diminution of eosinophiles in the blood at first, and then their increase as the bone-marrow, on the second day, began to react to the specific irritation. Recently v. Hoesslin[35] has reported a case in which the eosinophiles showed changes similar to those just described. The eosinophiles and lymphocytes both diminished during the attacks of asthma, the polynuclears increasing. As the attacks waned there was a rapid increase of the two first forms and sinking of the polynuclears below normal. The eosinophiles during these periods reached 10 per cent. Aubertin and Ambard[36] performed experiments on dogs to determine if eosinophiles, especially in the alimentary tract, are formed *in situ* or in the blood. After injection of secretin they found that eosinophilia of the blood (9 per cent., of which 1 per cent. were mono-

[31] Jour. Exp. Med., 1898, vol. iii, p. 315.
[32] Centralbl. f. allg. Path., 1893, Band iv, p. 529.
[33] Beiträge z. path. Anat. u. allg. Path., 1900, Band xxviii, p. 150.
[34] Münch. med. Woch., 1906, Nr. 17, p. 797.
[35] Ibid., 1907, Nr. 44, p. 2183.
[36] Compt.-rendus Soc. de Biol., 1907, t. lxii, p. 263.

nuclear) persisted for three months and without the presence of eosinophiles in the intestinal wall, where they appear in large numbers during digestion, unaccompanied by any appreciable increase in the blood. In addition to the hemic eosinophilia, the spleen was enlarged and showed marked myeloid transformation, containing large numbers of myelocytes and polynuclear eosinophiles. This, in connection with other similar studies, inclines these writers to believe that all eosinophiles are formed in the marrow or spleen.

Reference to the accompanying table will show that in the reported cases with autopsy the findings in regard to eosinophile cells have been variable. Not only is this true of their presence and numbers in the bronchial lumina and walls and in the alveoli, but also of their type. In one of Fraenkel's cases, for example, they were largely mononuclear; in mine, all polynuclear. Equally dissimilar findings have been recorded in sputum studies. I cannot see that these eight cases throw the least light upon the origin and significance of these cells in bronchial asthma. That they are not specific for this affection has been abundantly shown, although Predtetschensky is inclined to regard their enormous numbers as savoring of specificity. If some of the writers here quoted, Stschastnyi in particular, are correct in their theories of the local origin of eosinophiles, the possibility is suggested of finding those cells in the pulmonary tissues in cases of local or general chronic circulatory disturbance in the lungs, especially when accompanied by apparent interference with the vagi. It may be, however, that in most chronic affections phagocytosis is in abeyance regardless of the increased hemolysis accompanying such conditions. The study of large series of lungs exhibiting varied lesions should throw some light upon this question. Such studies now being made by me have already led to interesting results, regarding which I hope to make a further communication.

The so-called Charcot-Leyden crystals found in many cases of bronchial asthma are likewise not characteristic of any special disease, being found in the blood, spleen, and bone-marrow in cases of leukemia, in nasal polyps and other tumors, in normal marrow, pus, feces in cases of helminthiasis, and in other tissues under certain conditions. They also appear, but less often than in asthma, in other pulmonary affections, as emphysema, bronchitis, and tuberculosis. Their origin and significance are uncertain. Hyneku[37] believes they arise principally in eosinophile leukocytes through degeneration of their spongioplasm. In this view he is supported by Predtetschensky, and Kaufmann regards it as a possibility. Müller's opinion, that they are the crystallization product of a substance in the tissues, has already been cited.

[37] Quoted in Schmidt's Jahrbücher, 1907, Band ccxciv, p. 157.

In conclusion, it must be said that the pathological anatomy of bronchial asthma, as revealed in these eight cases, constitutes no exposition of the cause of the disease. The findings furnish a fairly satisfactory explanation of some of the clinical features, especially distention of the lungs and dyspnœa, and locates the source of some of the constituents of the sputum. Why those substances are formed is not clear. Further, and this point is of paramount interest, the histology furnishes no explanation of why the formation of such substances in the lungs in these cases gave rise to the clinical phenomena designated as bronchial asthma, while in other cases, with the presence of essentially identical materials, that symptom complex is lacking. The mucus, bronchial epithelium, leukocytes, eosinophile cells, Charcot-Leyden crystals, and spirals discharged from or found in the respiratory tract in cases not clinically bronchial asthma, are, it is true, not invariable in quality and quantity, but neither are they in asthma itself. We are consequently forced to regard the latter affection as the result of a cause as yet undemonstrable by studies of the lungs of these subjects. Inquiries as to the location and nature of this cause have led clinicians to advance the theories mentioned in the introductory paragraphs. Further discussion of these theories is beyond the scope of this paper, which deals only with the actual pathological anatomy of the disease in question.

HENRY GRAY, ANATOMIST: AN APPRECIATION.

By Frank K. Boland, M.D.,
of Atlanta, Georgia.

In reading a little book entitled *The World's Anatomists*, and written in 1905 by Dr. G. W. H. Kemper, I was struck by the fact that the only mention of Henry Gray is the date of his birth and death, and the statement that he was an Englishman and the author of a text-book on anatomy. This seemed but meagre notice, indeed, of a man whom medical students and physicians for a half century have been accustomed to think of as a most distinguished anatomist; and I resolved to find out more about him if I could. Surely a man must have been very little short of a genius to have written in his time the book he did at the age of thirty-one years. Today most of us have only begun to live at thirty-one; but Gray had accomplished more at that age than the great majority of us can hope to accomplish if we live twice as long.

Although dead less than fifty years, so little information concerning Gray's life has been published that an air of mystery seems to have

developed about the young man. This is accounted for in part by his early death and by the fact that he left no direct descendants to record the particulars of his career. These circumstances made the search for data an especially interesting, although difficult, task. I wished to know something of Henry Gray's life and to ascertain how much of Gray *is* Gray. The year 1858 was too late for one to make any great discoveries in anatomy, but a method of presenting the subject could be original, as could descriptive names and expressions.

The facts here given come through the courtesy of Mr. Robert Harrison, assistant secretary of the Royal Society, of which Gray was a member, and Mr. E. I. Spriggs, dean of the St. George's Hospital Medical School, Gray's alma mater, who secured for me the aid of Mr. C. T. Dent, the senior surgeon, to whom I am indebted more than to any one else. Mr. Dent gathered information from various records, and from interviews with Mrs. Stonhill, one of the two surviving relatives of Henry Gray, from Mr. Pickering Pick, one of the editors of the *Anatomy*, and from others of the few living contemporaries of the author. Without the assistance of Mr. Dent, this sketch would have lacked much of its detail.

Henry Gray was born in 1827, in London, probably, although it is not stated positively. His father was private messenger to George IV and William IV. He had one sister, who died at the age of twenty-one years, and two brothers. One brother died young; the other was Thomas William Gray, who had two daughters, one of whom is Mrs. Stonhill. This lady can give but little information about her uncle, so that where he passed his boyhood and where he received his preliminary education is not known. The date of his father's death is not on record, but young Gray does not seem to have been beset with the financial obstacles which so often handicap men of talent. His student and professional course to success was uninterrupted. There are now but few survivors who were his contemporaries at St. George's Hospital, and they appear to know nothing of his career previous to his entrance as a student.

Gray's signature appears on the pupil's book at St. George's Hospital, as entering on May 6, 1845, as a "perpetual student." This term, although probably customary, serves to illustrate the earnestness with which the eighteen-year-old youth took up his chosen work. At this time there was no medical school within the hospital precincts, but some rooms had been rented in Kinnerton Street, not far from the hospital, and it was there that the teaching in anatomy, physiology, and the other rudimentary branches was done. The lectures on medicine, surgery, and the clinical part of the curriculum were given at the hospital. Mr. Henry Charles Johnson, who was assistant surgeon to the hospital from 1843 to 1853, is believed to have been the lecturer on anatomy when Gray matriculated.

There is no evidence to support the absurd story that Gray was a poor student and failed in some of his examinations; the facts tend to prove the very opposite. In 1848, at the age of twenty-one years, he was awarded the Triennial Prize of the Royal College of Surgeons of England for a paper on "The Origin, Connection, and Distribution of the Nerves of the Human Eye and its Appendages, Illustrated by Comparative Dissections of the Eye in the Other Vertebrate Animals." Although this prize was first instituted in 1822, it has had only eight recipients.

Young Gray assuredly possessed great talent and untiring energy. The opinion of all those who remember him agrees in describing him as a most laborious and methodical worker, and one who learned his anatomy by the tedious but invaluable plan of making his dissections himself. Judging from the results he obtained, he had no time for anything but his work.

In June, 1850, he was appointed house surgeon to St. George's Hospital, which position he held for the customary twelve months. On June 3, 1852, he received the distinction of being elected a Fellow of the Royal Society at the remarkedly early age of twenty-five years. His hospital record and his activities in original research must have been highly esteemed to have secured him such honor. It has been supposed that he obtained the title largely through the influence of Sir Benjamin Brodie, who became president of the Royal Society in 1858. But Brodie himself was only elected a member of the Society in 1849, and does not appear even to have supported the candidature of Gray, although no doubt he took a warm interest at that time in so promising a pupil of the hospital. Brodie ceased to be surgeon to St. George's Hospital in 1840, but continued his active interest in the medical school, and, indeed, advanced the capital for the purchase of the lease of the buildings in Kinnerton Street.

Gray won the Astley Cooper Prize of three hundred guineas in 1853 for his dissertation on "The Structure and Use of the Spleen," a work which ranks next in importance to his *Anatomy*. This prize is awarded triennially, and is open to the world, students of Guy's Hospital alone being debarred from competing. Other papers which Gray had written up to this time were: In 1850, "On the Development of the Retina and Optic Nerve, and of the Membranous Labyrinth and Auditory Nerve;" in 1852, "On the Development of the Ductless Glands in the Chick;" and in 1853, "An Account of a Dissection of an Ovarian Cyst which Contained Brain."

From 1853 to 1858 he was lecturer on anatomy at St. George's Hospital. It is also recorded that he was surgical curator of the Pathological Museum during this period. No doubt his services as demonstrator of anatomy were very much in demand, for he had established a considerable reputation while a student. His time

must have been given very largely to the dissecting room, and we learn nothing of his experience in clinical work.

Gray now devoted his energies to the preparation of the work by which he is really known, the masterpiece, *Anatomy, Descriptive and Surgical*. Since this work is the only one of its kind which has come down to us from this time, the idea exists that no good books on the subject had been written before. Nothing could be more erroneous. Many excellent anatomies were in common use at the time Gray's made its appearance, and the new work was pitted against keen competition. Quain and Sharpey's *Anatomy* was probably the most popular book, although others, such as Wilson's and Winslow's, and the translations of the French writers, Cruveilhier, Bichat, and Cloquet, had strong following.

Gray undoubtedly felt that there was room for improvement in these treatises, particularly in the matter of arrangement and illustrations. He had a good conception of the principles of pedagogy, and desired, in so far as he could, to smooth for his students the hard road to anatomical knowledge. A comparison of Gray's work with that of his predecessors shows that he achieved his purpose in an admirable manner. He was not the Father of Anatomy, and it was not the presentation of any new anatomical discoveries, but the clearer and more systematic presentation of old ones, backed strongly by unparalleled drawings, which secured for his book its phenomenal success.

To Dr. H. Vandyke Carter, who made the drawings, a large part of the credit for the success of the work must be given. Gray, in the preface to the first edition, which is dated August, 1858, "gratefully acknowledges the great services he has derived, in the execution of this work, from the assistance of his friend, Dr. H. V. Carter, late demonstrator of anatomy at St. George's Hospital. All the drawings from which the engravings were made were executed by him. In the majority of cases, they have been copied from, or corrected by, recent dissections, made jointly by the author and Dr. Carter." In this preface, "the author also has to thank his friend, Mr. T. Holmes, for the able assistance afforded him in correcting the proof sheets in their passage through the press." According to Mr. Dent, the assistance that Mr. Timothy Holmes afforded was considerably more than might appear from this acknowledgment. Mr. Holmes had the literary gift developed to a very high degree. Mr. Dent thinks that the literary excellence of the first edition of the anatomy was mainly due to Mr. Holmes' suggestions, but this does not detract at all from the scientific value of Gray's work as an anatomist, or from the skill shown in the arrangement of the text.

The first edition was published by John W. Parker & Son in 1858, and was the only edition that Gray ever saw. The book was a success from the first. Such clear treatment of descriptive anatomy

had not been known before, and there has been but small improvement, except for additions, made in it since. The introduction of the remarks on surgical anatomy was the first ever attempted by an English author, and proved to be a popular feature.

The cuts far exceeded in number and excelled in accuracy and vividness any which had appeared previously. It is astonishing to see how many of these drawings are in the *Gray* of today. Indeed, very few of them have been discarded, wherein good judgment has been displayed, because as diagrammatic representations they would be hard to surpass, and such representations are more readily grasped by the student than any other.

Nevertheless, the critics were by no means unanimous in their praise. The *Lancet*, in its review, spoke in the most favorable terms, but the *Medical Times*, which was then the chief rival of the *Lancet*, took an altogether different view, its reviewer indulging in what was then known as a "slashing criticism." Gray was accused of freely borrowing from Quain and Sharpey's *Anatomy*. This work was the text-book then commonly in use, and the student was likely to saturate himself with it as succeeding generations have saturated themselves with Gray's *Anatomy*.

There is no doubt that many passages could be cited in which the phraseology very closely resembled that of Quain and Sharpey. But we know, without question, that most of Henry Gray's work was done from actual dissections. After all, anatomical descriptions cannot vary greatly, and it is more than probable that in the passages quoted by the critics, Gray was borrowing quite unconsciously when he described the dissections that were actually before his eyes.

Parker & Son's business was bought up by Messrs. Longmans, and the second and all succeeding English editions of Gray, now numbering sixteen, were published by the latter firm. This was a potential factor in the perpetuation of the work, since this firm has long been known as one of the most enterprising of publishers.

Even prior, however, to Longmans' purchase, the firm of Blanchard & Lea, now Lea & Febiger, of Philadelphia, had arranged with Parker & Son for the publication of Gray's *Anatomy* in this country. As Longmans' purchase was subsequent and subject to the arrangement of Parker & Son with Lea & Blanchard and their successors, the longest connection between the book and any of its publishers enures to the credit of America. During this long period the firms of Longmans and of Lea & Blanchard and their successors have cordially coöperated for the benefit of the book and its readers. It is not too much to say that the services of many of the most distinguished anatomists of the English-speaking race on both sides of the Atlantic have been enlisted in successive revisions.

Mr. Holmes became the editor after Gray's death, and subsequently Mr. Pick, both of whom were friends of the author and lecturers on anatomy and surgeons to St. George's Hospital. The

book has been doubled in size, and altered by English and American editors, but much of the original matter can be distinguished, especially in the arrangement. For example, the method of showing the relations of arteries by the ring with the adjacent structures grouped around it, so simple and yet so helpful, still remains as in the first edition.

In 1861 Gray was a candidate for the post of assistant surgeon to St. George's Hospital, two vacancies having at that time occurred. He would certainly have been elected, but unhappily was attacked by confluent smallpox, which he contracted while looking after his nephew, who had fallen a victim to the same disease. After a very short illness, Henry Gray died on June 13, 1861, at the age of thirty-four years.

He was at work on the second edition of his book at the time of his death, and had made good progress with a work on *Tumors*. The manuscript of this cannot now be found, and no part of it was ever published. Before his death Gray had been made a Fellow of the Royal College of Surgeons by examination, and surgeon to St. James' Infirmary.

These are the facts concerning Henry Gray's life as I have been able to gather them. They are no doubt genuine, but I trust their publication will be the means of bringing to light much more about such an inspiring character. I much regret that I could not learn more of the personal side of his character. His portrait shows the face of a man who might have been a great artist; the forehead is high and broad, the eyes are set widely apart, and the chin is powerful. Altogether his appearance commands attention, and we know at a glance that he was no ordinary person.

There is nothing recorded about his ability as a diagnostician or operator. The plan of his professional career, which is worthy of emulation, seems to have been first to ground himself thoroughly in the fundamental branches of anatomy and pathology, after which he would be equipped for the best possible work in the field of practical surgery.

He was about to quit the dissecting room for the operating amphitheatre when his life was brought to a sudden close. Sir Benjamin Brodie must have had this in mind when writing the letter reproduced herewith.

Of the estimation in which Gray was held at the time of his death, this letter furnishes eloquent testimony. Sir Benjamin Brodie was Sergeant-surgeon to the Queen, and one of the most distinguished of English surgeons, and it was to him that Gray dedicated his *Anatomy*. Brodie was nearly blind at this time, and very seldom wrote; indeed, this letter was probably the last that he ever put on paper. The latter was addressed to Mr. Charles Hawkins, one of the governors of St. George's Hospital, and his literary executor. The lady therein referred to, whose name is illegible, must have been

the one to whom Gray is said to have been engaged at the time of his lamented decease. A fac simile in my possession, which is difficult to decipher, reads as follows:

JUNE 15, 1861.

MY DEAR SIR: I am much grieved about poor Gray. His death, just as he was on the point of obtaining the reward of his labors, is a sad event indeed. If you have any means of doing so, I wish that you would express to Miss —— how truly I sympathize with her in her affliction. Gray is a great loss to the hospital and the school. Who is there to take his place?

Yours ever truly
B. C. BRODIE.

From this brief study of the life of Henry Gray, which was undertaken with the purpose of determining his true place in medical history, I am happy to conclude that he is entitled to the fame that is his. Although confessedly the glamour of renown has been augmented by clever illustrators, able editors, and progressive publishers, yet we could not fairly snatch away a single ray when we consider the part he played in the time allotted him. These factors are always instrumental in the success of such work.

Gray's genius, like that of many others, consisted of hard work and singleness of purpose; could he have lived long enough to carry this with his spirit of investigation farther into medical science, it is reasonable to believe that he would have left a name as great as surgeon as it is as anatomist and teacher.

REVIEWS.

1. Le Cancer: Prophylaxie, Etiologie, Traitement. By C. Sobre-Casas, Médecin à l'Hôpital Rawson (Buenos Ayres). Pp. 219. Paris: G. Steinheil, 1908.
2. Cancer: Relief of Pain and Possible Cure. By Skene Keith and George E. Keith, authors of a *Text-book of Abdominal Surgery*, etc. Pp. 155. New York: The Macmillan Co., 1908.
3. The Conquest of Cancer. By C. W. Saleeby, M.D., Pp. 361. New York: Frederick A. Stokes & Co., 1907.

The study of cancer is no man's field. That the whole medical world is engaged upon the problem is almost a platitude, for its verity; and the multitudinous publications, varying from profound to vagaries, necessarily include observations and speculations dealing with the most varied aspects of the question. That eventually there must be a conclusive answer to the great question as to the nature and origin of cancer, and that this must lead to a more nearly perfect idea of its treatment, cannot be doubted; and there is no telling whether success will come by the systematic elaboration of any one of the existing theories or whether it will be brilliantly exhibited by new lines of inquiry. It is safe to say, at least, that at the present no conscientious effort along any reasonable line can be disregarded as improper. All of three books herewith reviewed, therefore, are worth consideration, although they differ most widely in their attitudes and in the impressions which they leave upon the professional reader.

Dr. Sobre-Casas' brochure attempts in systematic fashion to review the general field of the present aspect of the subject, without any pretence toward elucidation of the obscure problems of the pathology of cancer or of advancing any specific measures for its cure, but rather of condensing the more important contributions upon the etiology of the malignant tumors and what has been written concerning prophylaxis and treatment. It thus seeks to give a convenient basis, a sort of stock-taking, to facilitate comparison and permit of more intelligent procedure into further study. After a brief introductory chapter upon prophylaxis, in which a plea is made for education of the public to the danger of postponing proper examination

of suspicious growths, the author outlines the work in Europe, this country, and his own as far as organization of systematic studies and provision of special hospitals and laboratories for the care and investigation of cancer are concerned. A cursory review of the various non-parasitic theories, and a somewhat fuller consideration of problems relating to a possible parasitic origin (with more particular details as to evidence of spontaneous inoculations and experimental transmissions) are succeeded by a brief reference to various causes which apparently are contributory to the development of cancer, as age, profession, traumatism and chronic irritations, heredity, arthritism, alimentation, arsenic, the influence of races, and the disproportionate frequency of cancer in certain localities. A suggestive but very brief part of this chapter deals with the actual physiological state of the host of advanced cancer, notably the atrophic condition of the heart and other organs and the alterations of the blood. The chapter upon treatment in turn takes up the surgical means and the results of surgical measures in cases of cancer in various parts of the body, a long list of physical and chemical measures and agents which have been advocated at one time or another and their results, a discussion of the ten or more serum methods which have been advocated in the hope of specific results, together with a brief consideration of palliative means. A short chapter upon general hygiene in cancer and a few pages of summation are succeeded by a biographical reference list fairly representative of European writers.

M. Sobre-Casas is optimistic as to the future of the work against cancer. The volume is the *resume* of his studies made in the course of a mission in Europe authorized by the Argentine Govenment, with the purpose of directing further work in Argentine, where, as elsewhere, the proportionate number of cancerous cases is on the increase. While he adopts the aphorism "early diagnosis, immediate operation," he looks forward to the attainment of a specific means of treatment, and clearly inclines to some form of parasitism as the causative agent of malignant tumors. The book, however, is a very fair and a reasonably conservative, and, at the same time, a widely inclusive, *resume* of the subject. It is valuable for the purpose set the author, and reflects credit upon him in the performance of his official mission. There are numerous inaccuracies in spelling and some in typography, which mar the general tone of the volume.

The Keiths' little volume, largely occupied with the histories of cases of cancer illustrative of the effects of a method of treatment advocated by the authors, has as its prime purpose the establishment of the belief indicated in its title. The procedure in question is nowise to be substituted for the early surgical ablation of cancerous tumors, but is urged in those instances in which operative measures cannot for one reason or other be undertaken, and as an adjuvant

when this is desirable. The authors have no theories to advance, and have little that is good to say of specific medications. Their method consists simply in the employment of a combination of arsenic and iodine, both long known and of some repute as medicinal agencies in the treatment of malignant disease. Their combination is an emulsion containing iodipin, arsenate of iron, cacodylate of iron, and cinnamate of sodium, mixed according to directions stated in the volume, but not so clearly as might be wished. It is administered hypodermically in the arm, buttocks, abdominal wall, or other part as desired, and there is some variation among individual cases as to the degree of tolerance found and the resultant value. The authors claim from the use of the remedy, now employed for some years by them, a distinct prolongation of life, general physical improvement, and a very decided relief from pain, particularly when this symptom is in the cancer and due actually to it, rather than to pressure by the tumor mass or to ulceration or other complication. They believe that there is less tendency toward recurrence when the combined drugs mentioned are employed after operation, and they express a hope, which, however, they are unwilling to rely upon, that in selected cases it may be curative. Two-thirds of the volume is occupied by case histories of cancer and a few of sarcoma illustrative of the arguments of the writers.

It is probably as much a matter of habit among our British brethren as one of taste whether such a communication be accorded the dignity of a separate volume or take its chances as a journal article. Certainly the former offers the advantages of a greater exhibition of details of corroboration, and, if the measure advocated reach in other hands the same measure of beneficence as in the experience of the authors, no one may begrudge it or them the distinction afforded the subject by the neat presentation the publishers have given it.

Saleeby's is a book that the reviewer is disposed to believe would not take its present title, or make as insistent demands for acceptance, were it to be undertaken at the present moment. It is most attractively written, and is singularly persuasive in its arguments and verbiage, and is withal very suggestive and valuable from its sidelights upon the subject. But in its main purpose, the advocacy of an idea, it is today an unhappy outrunner of a theory which is unproved and but poorly sustained and lags behind this defending and promulgating volume. Dr. Saleeby seeks in his book to prove as of specific and general application among the malignant growths the idea of Professor Beard—and succeeds to his own satisfaction; and it is more the pity that the world's experience has not better fulfilled his expectations in the use of the specific medication for cancer which the theory is supposed to indicate. That there have been instances of cancerous growths in which the use of trypsin has been followed by cure is undoubted; but so, too, there have been

recoveries after the use of forty different other agencies which, superficially at least, have even less claims to be curative than has the pancreatic secretion. That there have been failures from the use of trypsin, surely, in equal measure to the proportion of failures from the multitude of other cures, the days and months are constantly giving evidence. And it is essentially in this point that Saleeby has placed his justification, that the logical and presumably infallible remedy has been found; in which, therefore, he has also met his undoing. It would be an impertinence, even now after the failure of the trypsin treatment to establish its inherent correctness, to criticise in the same spirit and with the same lack of hesitancy the theory of the trophoblastic origin of tumors. In this Professor Beard is not contradicted, and the theory must await with the other theories, whether developmental, parasitic, or what-not, for a final answer, which does not as yet prevail. That trophoblasts, undifferentiated developmental cells of the segmentation body, are not completely utilized in the formation of the economy is assured; that some of these may be included in the forming embryo may likewise be accepted; that these disappear coincidentally with the formation of the pancreas (which, for that matter, nearly agrees with the formation of the hepatic diverticula as well) is a contribution which Beard makes, and is of necessity a matter of undoubted interest, but of unproved relation with the pancreas. That there are types of growth which singularly suit our ideas of the behavior of trophoblastic development as the various teratomas is true; and that there is a nice gradation possible to be made out (although it may be quite artificial and forced in one sense) between these and the ordinary types of malignant growths is also true; and, given a cell capable of indefinite proliferation and variable or even multiple differentiation, one can only accept the theoretical origin of a given type of cancer from it on the ground that differentiation of the cells does occur with proliferation. But in such case, in order to explain the unifomity of histology of primary cancers in different structures, one must aver an adapting influence of these parts upon the growing tumor cells; and when this is said, one is face to face with the further problem why the tissues about secondary tumors do not with equal power exert their power of adaptation upon the secondary foci. And inasmuch as the malignant teratomatous types give metastases which conform to their multiform progenitors, why do not the tissue in which they are lodged interfere with their polymorphous character and impose a specific type upon them? It is particularly on this point that Beard's theory of tumor formation differs from Cohnheim's embryoblastic theory, that is, in the question of the stage of differentiation of the tumor anlage; Beard's idea demands a cell as yet undifferentiated but capable of differentiation, Cohnheim's accepting the actual differentiation into cells of definite type in the anlage. In neither is it a vital objection that tumors are not of more

common occurrence in early than in later life; yet it is not unfair to regard this as a weakness of both theories from our present standpoint. If, as Cohnheim has indicated, according as the embryonal anlage of a tumor represents an early or a late separation or cellular excess, there should be a rapid or more slow rate of growth to characterize the tumors; one is given further reason for question why, if tumors arise from included trophoblasts with an undoubted inherent potentiality of very rapid proliferation, do these neoplasms show such variability in rate of growth; why are they not all of highly rapid growth? If it be the pancreas which destroys these aberrant trophoblastic cells in the economy and prevents their growth into tumors, why should there be no plainer relation between pancreatic failures of one sort or another and the occurrence of malignant disease? Why should there be cancer in the pancreas itself?

Such questions and objections are, to the reviewer's mind, entirely fair, and such matters and many more of the same type, some perhaps even more insistently, must be satisfied before final acceptance of the theory as more than a pure hypothesis for the general group of the malignant growths. But it must at once be acknowledged that, so far as the part of the trophoblast being the basis of origin is concerned, and shorn of the pancreatic relation and the insistence that trypsin is the necessary cure-all of cancers, there are practically as many points of favor of the theory as of any of the developmental theories. That these tumors are not the result of parasitism, but are themselves the parasites, has strong reason for consideration, and that thus in a modified form, and perhaps limited to certain special types of malignant tumors, the theory may eventually come into definite favor cannot be gainsaid. The idea of chemical relations which is embodied in the supposition that the pancreas is the cause of the disappearance of the trophoblast in the embryo, and that it, therefore, is responsible for permitting the tumor growth by some kind of inefficiency in later life, is an application of the broad theory of hormones to this particular subject; and this, too, is worthy the most careful and prolonged inquiry. But that the pancreas is necessarily the point of origin of such chemical restrainers or chemical stimulants to growth entirely lacks proof. That the corpus luteum chemically stimulates the development of decidual cells, and may be potent in production of deciduomas, may be accepted as proved; and the principle probably has a wide range of applicability. Experience with pancreatic extracts in cancer gives but little reason to believe this organ either energizes or restrains proliferation of any of the tissues or cells liable to develop into cancer; but somewhere in the body there may well be structures which are responsible in this very fashion.

Such considerations, it seems to the reviewer, are more to the point in the consideration of this book than a detailed discussion of the book itself. The attitude of the author as an enthusiast, his

unwarranted and pettish criticism of the "authorities that be" for not seeing the same things in the same light as he does himself, his advocacy as a fact of a theory in its entirety which has not any more grounds for acceptance of its best parts than other existing theories, and plenty of contradiction in application of its practical phases—these are the unfortunate sides of the making of the book. That it is a well-made book, that it places in the most logical and appealing way the subject-matter before the reader, that it is suited, as the author intends, for the ready perusal and easy understanding by a wide group of the public as well as medical readers, must be acknowledged.

For the technique of the argument and presentation the author is to be complimented; for the insufficiency of his subject-matter and the failure of its high claims he is to be commiserated; but for his injudicious haste and misleading claims in the attempt to establish an enticing but untried theory as a working reality, there can be little but reprimand. A. J. S.

DIAGNOSTICS OF THE DISEASES OF CHILDREN. By LE GRAND KERR, M.D., Professor of the Diseases of Children in the Brooklyn Postgraduate Medical School. Pp. 542; illustrated. Philadelphia and London: W. B. Saunders Company, 1907.

IN this recent contribution to the already well covered field of pediatric literature, Dr. Kerr has satisfied a long-felt need. Students of pediatrics have searched in vain through the larger text-books on diagnosis for a satisfactory consideration of the subject as applied to diseased conditions in childhood. Whatever references may be found are either sketchy or wholly inadequate. Dr. Kerr's book, therefore, may serve not only as a supplement to previous works on general diagnosis, but also as a complement to the comprehensive text-books on pediatrics which have appeared within the last few years. A careful perusal of the book convinces us that Dr. Kerr is a thorough master of his subject, and a most inspiring teacher. His style is clear, forcible, and always interesting, and his methods of deduction are often novel and suggestive. Especial mention may be made of the sections on the acute infectious exanthemata, in which will be found, besides the careful working out of their diagnostic features, a statement of the principal complications to be looked for, and a study of their premonitory symptoms, the early recognition of which may mean so much in the final outcome of the case.

Dr. Kerr's work has been so well done that it seems ungracious to single out for criticism any expression of personal opinion or inadvertent statement; but the reviewer feels satisfied that in future editions, which are sure to come, some modification should be made in the statement that tuberculous meningitis is the commonest form of meningitis in childhood (p. 313). Clinical observation, aided by systematic study of the cerebrospinal fluid, certainly points to the greater prevalence of meningococcic infection, even in those cases of slower onset which suggest the picture of tuberculous meningitis that has become classic. But this is merely a friendly hint, without malice. Dr. Kerr has done an excellent piece of work, and we feel certain that the student and the practitioner as well, can learn more of pediatrics from its perusal than from the ordinary text-book. T. S. W.

THE CARE OF THE BABY. A Manual for Mothers and Nurses. By J. P. CROZER GRIFFITH, M.D., Clinical Professor of Diseases of Children in the University of Pennsylvania, Philadelphia. Fourth edition; pp. 425; illustrated. Philadelphia and London: W. B. Saunders Co., 1907.

THE appearance of a fourth edition of Dr. Griffith's well-known manual emphasizes the favor with which it was originally received, and a careful comparison of texts shows that little was found in the third edition that could be improved upon in the fourth, except in the illustrations, which have been increased by ten. An appendix of sixteen pages, however, has been added, covering briefly the general principles of feeding a healthy infant, intended for mothers who, of necessity, are thrown entirely upon their own resources when this important problem confronts them.

This book should long maintain its distinction as one of the best of its class. T. S. W.

PROGRESS

OF

MEDICAL SCIENCE.

MEDICINE.

UNDER THE CHARGE OF

WILLIAM OSLER, M.D.,

REGIUS PROFESSOR OF MEDICINE, OXFORD UNIVERSITY, ENGLAND,

AND

W. S. THAYER, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND.

The Blood in Myxœdema.—BENEE and ENGEL (*Wien. klin. Woch.*, 1908, xxi, 905) report the blood findings in 5 cases of myxœdema. Frequently a mild secondary anemia is present. The most marked alteration occurred in the leukocytic formula. Differential counts showed the following: polymorphonuclear neutrophiles 58 to 39 per cent.; lymphocytes 36 to 56 per cent.; eosinophiles 4.9 to 15.8 per cent.; mononuclears 2.4 to 8 per cent. The eosinophilic myelocytes were found. Thyroidectomized animals show a lymphoid metaplasia of the bone marrow and this, Benee and Engel say, explains the lymphocytosis. The eosinophilia they look upon as the result of positive chemotaxis from substances circulating in the blood. The total number of the leukocytes was normal (one case 12,400).

The Finding of Products of the Adrenals in the Blood and the Urine.—WATERMAN and BODDAERT (*Deut. med. Woch.*, 1908, xxxiv, 1102) doubt the accuracy of previously reported observations, in which adrenalin in increased amounts is said to have been found in the blood and urine of nephritics, leading to the assumption of a hypersecretion of the adrenals in this disease. They show that the ferric chloride test for adrenalin may be given by pyrocatechin and salicylic acid, bodies closely related to adrenalin which is methylamido-acetopyrocatechin. The colors vary a little with these substances, that with salicylic acid being more violet, but in the pigmented urine or serum the color tests are unreliable.

Using Ehrmann's test (dilatation of the enucleated frogs eye) they find that pyrocatechin is strongly mydriatic (1 to 500 in 0.9 per cent. NaCl solution). Resorcin, hydrochinon, and salicylic acid are less powerful mydriatics. They have had no experience with Meyer's

test (the bloodvessel of a freshly killed ox is placed in the solution to be tested; if it contracts, adrenalin is assumed to be present), but Schlayer reported negative results with this test, using the blood and urine of nephritics.

Waterman and Boddaert conclude that the presence of abnormal amounts of adrenalin in the blood and urine of nephritics is, as yet, not satisfactorily demonstrated.

"Duodenal" Diabetes.—EICHLER and SILBERGLEIT (*Berl. klin. Woch.*, 1908, xiv, 1172) based their study on a report by Zock, of two cases of gycosuria following the taking of alkali with suicidal intent. He observed that the duodenal mucosa was destroyed, while the pancreas remained uninjured. The production of a similar lesion is a dog also led to glycosuria, hence the assumption of a duodenal glycosuria in man and dog, the result of destruction of the duodenal mucosa.

Eichler and Silbergleit repeated Zock's experiment, using a somewhat different technique. After opening the abdomen aseptically, they injected 4 to 6 c.c. of concentrated sodium hydrate into the duodenum. Glycosuria resulted in 2 cases. In 2 other dogs glycosuria was produced by applying the Pacquelin cautery to the duodenal mucous membrane and destroying it. Other parts of the small intestine were next tried to see whether the action from destruction of the duodenal mucosa was specific. In 3 of 4 instances glycosuria ensued after lesions produced in the ileal mucosa. In all the dogs the pancreas showed nothing abnormal. The glycosuria was of short duration, disappearing on the fourth day after operation.

The authors look upon the plycosuria as being the result of the severe shock to the nervous system; the glycogen of the liver is thrown into the blood and is excreted in the urine. They conclude that it is not justifiable to speak of "duodenal diabetes" in man or dog.

Chyluria.—LÜDKE (*Münch. med. Woch.*, 1908, lv, 1369) reviews the cases of non-parasitic chyluria reported in the literature and reports one new case, which followed a colon bacillus cystitis. No etiological factor could be found. There was no chylemia; diet had no effect in increasing or diminishing the fat content of the urine. The daily excretion of fat in the urine amounted to 6 to 8 grams. The prognosis is not unfavorable. No effective remedies are known. The condition is very rare.

A New Function of the Pancreas and its Relation to Diabetes Mellitus.—LOEWI (*Arch. f. exp. Path. u. Pharmakol.*, 1908, lix, 83) has studied the mydriatic action of adrenalin in animals after the extirpation and after partial destruction of the pancreas in cats and dogs. In these animals normally one finds no mydriasis after instillation of adrenalin solutions. When the pancreas has been extirpated, he finds that adrenalin solution now has a mydriatic effect. Partial destruction of the pancreas gave inconstant results, mydriasis being present in some instances—absent in others. Loewi now instilled adrenalin into the conjunctiva of man. Three drops of 1 to 1000 adrenalin solution was used and the dose was repeated in five minutes. The pupil was carefully measured; the results showed, however, that when mydriasis

occurred it was visible to the unaided eye. In 36 cases—healthy adults, as well as those suffering with nephritis, carcinoma, tuberculosis, anemia, icterus, heart disease, adiposity, pneumonia, tabes, and rheumatism—no mydriasis was observed. Of 3 cases of Basedow's disease, 1 showed a marked dilatation of the pupil, due, the author believes, to increased irritability of the sympathetic. 18 diabetics were now examined. In 8 cases the instillation was without result; these included mild and severe diabetes: 1 patient in coma who had previously given a positive response, and 1 case of diabetes with acromegaly. In the 10 remaining cases of diabetes mellitus a marked dilatation of the pupil occurred within thirty to sixty minutes after instillation of the adrenalin, the cases ranging from mild to severe, including 1 in coma. Loewi concludes that (1) a positive test means pancreatic disease; (2) in a diabetic it indicates pancreatic diabetes; (3) the absence of the reaction does not exclude the pancreatic origin of the disease.

The Importance of Urobilinuria in the Diagnosis of Diseases of the Liver.—Fischler (*Münch. med. Woch.*, 1908, lv, 1421) has studied the cases of urobilinuria and urobilinogenuria in Krehl's clinic, with interesting results. Urobilin and urobilinogen are formed from bilirubin in the intestines by the reducing action of bacteria. Both are absorbed and carried again into the liver. Fr. Müller's observations are the basis of subsequent work; in a patient with complete closure of the ductus choledochus, he showed that there was abundant bilirubin, but no urobilin. The patient was then given bile by the stomach tube, and in three days urobilin was found in the urine in addition to bilirubin. The same results have been obtained experimentally in dogs. Normally, urobilin and urobilinogen are absent from the urine or are present only in traces. They are found in the urine practically only in those conditions in which the liver is diseased, according to Fischler's observations. The tests for these bodies are of importance in the diagnosis and prognosis of obstructive jaundice, since they enable one to determine whether any bile enters the intestine. In Laennec's cirrhosis of the liver these bodies are always present in the urine, and their presence or absence may be important differential diagnostic signs of this disease. So, too, in chronic passive congestion of the liver, acute infectious diseases, pulmonary tuberculosis, the presence of urobilin indicates that the liver is diseased.

The Spectroscopic Determination of Blood in the Urine.—Schumm (*Münch. med. Woch.*, 1908, lv, 1488) calls attention to several points which may prove helpful in detecting minute quantities of blood in the urine. In making spectroscopic examination of the urine for blood, he points out that it may be recognized in quantities as small as 1 to 2000, when the urine is contained in the usual test tube; if the layer of urine through which the light must pass is made much thicker, the delicacy of the test is greatly increased. Thus when urine is put into the usual polariscope tube of 20 cm. length, the bands of oxyhemoglobin may be recognized in a dilution of 1 to 25,000 (amounting to about one drop of blood in the twenty-four-hour urine). If oxyhemoglobin has been changed to methemoglobin or hematin, the urine must first be extracted and then examined for the bands of hemochromogen.

The Stomach Contents in Gastric Carcinoma.—H. FISCHER (*Deut. Archiv f. klin. Med.*, 1908, lxxxiii, 98) studied protein digestion produced by the gastric juice, obtained from 2 cases of carcinoma of the stomach, each a year old. Normally, the gastric juice does not split protein to diamino-acids, and it is as yet unsatisfactorily shown that monamino-acids are formed. In gastric carcinoma, on the other hand, Fischer has demonstrated that a ferment is present capable of splitting the proteins into mono- and di-amino-acids. This, then, may prove of value in the diagnosis of gastric carcinoma, after a simpler technique for the recognition of di-amino-acids is found. The puzzling HCl deficit in gastric carcinoma is also explained by Fischer's experiments. Emerson's experiments seemed to show that alkaline bodies arise in gastric cancer, but at that time Emil Fischer had not demonstrated that the protein molecule is formed of amino-acids linked together (smaller groups, peptids). In carcinoma the HCl unites with the amino radicle, the body thus formed reacting acid to litmus, whereas, the peptid ununited with HCl is alkaline to litmus. The result in gastric carcinoma is that the total acidity increases, free HCl disappears; indeed a point is reacted where the HCl present no longer suffices to satisfy all the free amino groups, that is, where HCl must be added to neutralize the amino-radicles before the reaction for free HCl is obtained.

The Use and Value of Tuberculin in the Diagnosis of Pulmonary Tuberculosis.—L. HAMMAN (*Archiv. of Inter. Med.*, 1908, i, 443), after a complete review of the previous literature of this subject, gives in detail the results in many cases of the subcutaneous, eye, and skin tuberculous reactions and concludes that while tuberculin is a valuable aid in the diagnosis of pulmonary tuberculosis, it must be used with care and the results interpreted with caution. The reaction is specific, and it must be borne in mind that a very insignificant lesion may produce tuberculin hypersensitiveness; the prevalence of such lesions should be fully realized. A negative, reaction is decisive information as is also a focal reaction. In the absence of a focal reaction, tuberculin hypersensitiveness must be valuable as one phase of the clinical picture, and our judgment not too much warped by its presence. The cutaneous reaction is too delicate an indicator to be of any value in diagnosis unless the reaction be negative, which it seldom is in adults. The eye reaction gives results more nearly in accord with clinical experience, but by no means absolutely certain, and Hamman feels that it cannot supplant the subcutaneous method. In comparing the last two methods, they should not be used simultaneously; the eye inoculation should precede the subcutaneous by at least a few days.

The Gastric Secretion in Nephritis.—ENRIQUEZ and AMBARD (*Sem. méd.*, 1907, xxxv, 409) note that deprivation of salt in diets has an effect on the gastric secretions both in cases of hyperchlorhydria and hypochlorhydria, causing, in both instances, a drop or increase in the hydrochloric acid and so a return to the normal secretion or thereabouts. Enriquez and Ambard claim that every nephritis has a more or less marked influence on the gastric secretion. In very slight kidney lesions there is usually manifested a hyperchlorhydria, this being most probably due to the excess of salt in the body which salt stimulates the

gastric secretion. Retention of salt then increases the secretion and deprivation of salt reduces it, as has been shown experimentally in dogs. In more severe nephritis with albuminuria, however, the retention of salt alters the gastric secretion, but this excess of salt has an irritating effect on the stomach as on the kidneys; this irritating and therefore depressing action overcomes the stimulative action which would produce a hyperchlorhydria and so hypochlorhydria results. The deprivation of salt then allows the stomach mucosa to recover its tone and overcome this depressant action even before the general salt balance throughout the body is restored. Thus dechloridation may be followed by a slight, transient hyperchlorhydria. Enriquez and Ambard believe that the effect of salt deprivation on altered secretions of the stomach opens up a new field for the study of its many diseases, and may have great influence on some of the modes of treatment in gastric disorders which at present have no apparent connection with each other.

Excretion of Urotropin in the Bile and Pancreatic Juice.—S. J. CROWE (*Johns Hopkins Hosp. Bull.*, 1908, xix, 109) notes that for many years substances excreted in the bile have been more or less carefully studied in the hope of finding a suitable antiseptic capable of being excreted in sufficient strength to act favorably in injections. The part played by the typhoid bacillus in the gall-bladder, whether as an infective agent, as in the dangerous chronic carriers of disease, or as the starting point of gallstones, led Crowe to experiment with urotropin (hexamethylenamen), which has been already used so successfully in bacilluria and can so easily be detected by tests. In the animals experimented upon it was found that urotropin, when administered by mouth, was rapidly absorbed and remained in the circulating blood twenty-four hours, with a maximum concentration five to eight hours after giving the drug. In dogs it is excreted in the bile, pancreatic juice, and directly through the wall of the gall-bladder. It was found to be present in the saliva and milk of dogs after the intravenous injection of 1 gram. With this experimental data at hand Crowe was able to study the effects of this drug on several surgical cases with biliary fistulæ. These cases showed a rapid disappearance of the organisms from the infected bile following the use of the drug, and the fistulæ closed rapidly. In another case in which the injection was made into the cerebrospinal fluid, and in one case of gonococcal arthritis the infection rapidly cleared up on the administration of the drug. Crowe was able to demonstrate its excretion in the bile, cerebrospinal fluid, saliva, pleural exudate and the blood in man; he also found that after single large doses, 75 grains per diem, it appears in the bile in quantities which exercise a decided bactericidal action. The large doses in the cases studied caused no gastric symptoms or no hematuria, but in one case there developed painful and frequent micturition which stopped promptly on withholding the drug for a few days. Crowe believes that the drug may be of great value in acute affections of the gall-bladder, as a prophylactic in typhoid convalescence, against the possible subsequent formation of gallstones or the development of chronic bacillus carriers, and, lastly, as a general prophylactic before gall-bladder operations.

SURGERY.

UNDER THE CHARGE OF

J. WILLIAM WHITE, M.D.,

JOHN RHEA BARTON PROFESSOR OF SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE UNIVERSITY HOSPITAL

AND

T. TURNER THOMAS, M.D.,

ASSISTANT SURGEON TO THE UNIVERSITY AND THE PHILADELPHIA GENERAL HOSPITALS, AND INSTRUCTOR IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA.

Concerning the Experimentally Produced Ulcer of the Stomach.—CLAIRMONT (*Arch. f. klin. Chir.*, 1908, lxxxvi, 1) says that up to the present time no one has succeeded in producing, experimentally, a gastric ulcer in animals. By the excision of a piece of mucous membrane, and cauterization with acids (Fibich), stomach defects result which never fail to heal and, therefore, do not develop into genuine gastric ulcers. In the cardiac half of the stomach the healing occurs more rapidly, as a rule, in three weeks the defects are covered with epithelium, than in the region of the pylorus where the cicatrization is concluded usually in six or seven weeks. Either by a simultaneous or a later performed gastro-enterostomy, the process of regeneration is favorably influenced and leads to a more rapid healing of the defect regardless of what portion of the stomach it may involve. Fibich's view, that a gastric ulcer after a gastro-enterostomy heals like a fresh defect in the mucous membrane in a few days, is not supported. The postoperative treatment, after a gastro-enterostomy, must take into consideration that the ulcer still remains and that it must gradually become cicatrized.

Concerning the Orgin of Lateral Cervical Fistulæ.—WEGLOWSKI (*Zentralbl. f. Chir.*, 1908, xxxv, 426) says that the lateral cervical fistulæ are very similar in formation to the median fistulæ. In both there may be several lumina and in both the lining is usually of cylindrical epithelium, although several layers may be found. Lymphoid follicles, mucous glands, etc., are found in their walls. While the median fistulæ are recognized as developing from the thyroglossal duct, the lateral are considered as originating from the branchial clefts. This latter theory does not explain why the external openings are found only along the anterior border of the sternomastoid muscle, and why it is found at times at the angle of the lower jaw, at times at the sternum. Nor does it explain, why, with an opening for example in the middle of the neck, its course is not always upward, but often downward toward the sternum. Weglowski made a series of investigations on embryos, as well as on cadavers, and found a complete analogy between both kinds of fistulæ. The branchial clefts disappear in the second month of embryonal life. From the first arch is formed the lower jaw, and from the remaining three arches are developed the body, horns of the hyoid bone, the styloid and similar muscles. The branchial apparatus is properly limited to

the region of the face, not to the neck. The hyoid bone determines the lower border of the branchial region. Neither the arches nor clefts can project themselves downward, and, therefore, remnants of them cannot be found in the neck. The abnormal situations of the external cleft with relation to the inner, which usually have been made to explain the etiology of these fistulæ, have not been observed in embryonal life. In the third week of embryonal life there appear two depressions which become canals leading downward. One springs from the third cleft, the other from the fourth. From the third is developed the lateral lobe of the thymus gland, and from the fourth the thyroid. Weglowski's investigations on the cadaver showed that in 14 per cent. some remains of the canals of the thymus gland were found from the throat to the sternum. Remains of the thyroid were found in only 2 out of 150 preparations. The conclusion is reached that the lateral cervical fistulæ arise not from the branchial clefts, but from the remains of the of the thymus and thyroid glands.

The Operative Treatment of Varicose Veins, Elephantiasis, and Ulcer of the Leg.—FRIEDEL (*Arch. f. klin. Chir.*, 1908, lxxxvi, 143) treats those cases of varicose veins of the lower extremity, which are not suitable for excision or the Trendelenburg operation, by a spiral incision. The varicose veins tend to increase in size and extent and may become imbedded in cicatricial tissue from repeated inflammation, and may become concealed in an extensive concomitant œdema producing an elephantiasis of the leg. Often the patient is weakened and run down. Previous ligature may have failed and the associated ulcers may refuse to heal under the usual hospital treatment. In such cases Friedel has obtained good results from the spiral incision of Rindfleisch. The operation is performed in suitable cases as follows: Anesthesia is produced by lumbar spinal injection. Then in all cases a piece of the saphenous vein is excised, and the course of the spiral incision is marked by a light stratch of the skin of the leg. If an ulcer has been or is present, its site is included between the spirals of the incision, above and below, the chief point is to divide all the varices, and, if possible, several times. The incision should begin high enough, usually just below the knee, and should go as low as necessary, usually to the dorsum of the foot. The closer the turns of the spiral incision are to each other, the more often the individual veins will be divided and the greater the possibility that the varices will be entirely removed. While Friedel was satisfied with two turns at first, he later employed five. Bad results, as skin necrosis, have not resulted from the close approximation of the spirals, and in the future he will probably place them closer together. In this way he hopes to remove almost entirely the pressure within the vessels. The extensive opening up of the lymph and connective-tissue spaces causes an enormous evacuation of the serum of the field of operation. This leads to a subsidence of the inflammatory symptoms, and a reduction of the swelling of the limb. The frequency with which the blood stream is broken gives greater security against recurrences.

An Operative Treatment for Obesity.—SCHULZ (*Mitt. a. d. Grenzg. d. Med. u. Chir.*, 1908, xviii, 776) says that he has found no published record of operation for obesity since Demars and Marx in 1890. He

reports good results in 2 cases operated on five and four and one-half years ago. The layer of fat in the abdominal wall is not equally thick in all parts. In the lower part, above the pubic and inguinal regions, it does not exceed in thickness more than about one inch. Elsewhere it varies widely. Where these two regions, one of constant the other of varying thickness of fat, meet, are two curved lines each passing from one anterior superior iliac spine downward and inward toward the pubis. The overhanging fat produces furrows at the lines, and is further forced downward in women by the use of corsets. The furrows mark the position of the lower transverse incision, the upper in the median line being two fingers' breadth below the umbilicus and passing to both sides well to the lateral portion of the back. The lower meets the upper at its ends. The intervening elliptical portion is removed down to the aponeurosis. The point in the median line, through which the upper transverse incision is to be made, is determined before the operation, while the patient is standing and the overhanging roll of fat can be best observed. When the patient is lying down this cannot be well determined. After the removal of the skin and fatty layer, included between the incisions, it will be seen that the thickness of the layer of fat in the upper cut surface is much greater than that in the lower. A wedge-shaped piece of the fat is removed from the upper wound surface, the incision for this being directed from the skin obliquely to the aponeurosis. The skin edge of the upper flap can then be drawn more easily toward that of the lower and the wound closed by sutures. Two drains are passed from the median line to the ends of the wound. A large amount of fatty material will escape through the drains. It this were retained it would favor suppuration. The operation is so easily carried out, there is so little danger associated with it, and the results are so good that in the future it should gain more general favor.

Treatment of Perforative Peritonitis.—MURPHY (*Annals of Surgery*, 1908, lxvii, 870) says that the importance of the peritoneum lies not so much in its great surface as in its tremendous power of absorption. There is early acceleration of absorption with slowing later on. I we can tide our patients over this period of accelerated absorption all will be well. The term "free" peritonitis should be used for the general, diffuse variety, and "circumscribed" for the encapsulated form regardless of the size. Of the typical symptoms, collapse is a later, never an initial, symptom. The patient should be placed in the Fowler position as soon as the diagnosis is made and kept so until convalescence is well advanced. The relief of pus tension is the first surgical step toward retarding absorption in all acute infections. Reduction of tension should be initial and the absence of pressure continuous. These are accomplished by drainage. The entire technique of these operations for peritonitis must be accomplished in a very few minutes, that is, get in quick and get out quicker. The retention of fluid (protoclysis) depends entirely on the method of administration. Opium and coal-tar products were never given in this series of 51 cases. Of these there were 6 of postoperative ileus; 2 were operated on for gastric perforations, 1 duodenal, 5 typhoid, and 43 appendiceal. One died of a double pneumonia on the sixth day after operation, and a second from mechanical ileus. The time elapsing between the perforation and the operation

varied considerably. In the duodenal case it was eight hours; in the gastric cases it was eight and fourteen hours respectively. In the appendiceal cases a period of forty hours was not exceeded, while many of them had suffered from the appendicitis, three, four, up to seven days. There was no death in the series of 51 cases from the peritonitis, *per se*.

Late Results after Operation for Benign Diseases of the Stomach and Duodenum.—MOYNIHAN (*Annals of Surgery*, 1908, xlvii, 873) made an analytical study of 281 cases upon which he had operated for non-malignant diseases of the stomach, up to the end of 1905. The following are some of the lessons to be learned from this study: The operative treatment of stomach disorders should be confined exclusively to those cases in which an organic lesion is present, such as a demonstrable and palpable ulcer of the stomach or duodenum or some condition which hampers the proper action of the stomach. When at operation a perfectly normal stomach is found, we must not cover our diagnostic failure by the performance of an unnecessary operation. In cases of acute perforating ulcer the perforation should be closed or the ulcer excised. When the ulcer is on the lesser curvature nothing more is necessary. When it is prepyloric, pyloric or duodenal, gastro-enterostomy also should be performed. When a non-malignant lesion is discovered the appropriate treatment depends upon its position in the stomach. An ulcer on the lesser curvature, some distance from the pylorus, offers no obstruction to the passage of food and should be excised. A gastro-enterostomy may give incomplete relief, and malignant disease may set in later. In some cases, however, when the ulcer is on the curvature or on the posterior surface of it, adherent to the pancreas, relief follows if gastro-enterostomy is performed on the cardiac side of the lesion. Gastro-enterostomy should be performed if the ulcer be perpyloric, pyloric, or duodenal. It should be infolded whenever possible to prevent hemorrhage and perforation. The most satisfactory method of gastro-enterostomy is the no-loop operation, with the almost vertical application of the bowel to the stomach. Regurgitant vomiting occurs as the result of the "loop" operation, whether anterior or posterior. It is relieved almost certainly by an entero-anastomosis. In cases of hour-glass stomach, the surgical treatment necessarily presents special difficulties on account of the frequency of two lesions: one in the body of the stomach and one at the pylorus, and double operations have to be frequently performed.

A New Method of Diagnosis and Treatment of Fistulous Tracts.—BECK (*Zentralbl. f. Chir.*, 1908, xxv, 555) injects a bismuth-vaseline, a paste of a fluid consistency, under aseptic precautions, by means of a glass syringe, into the fistulous tract under considerable pressure. By the skiagraph he is then able to trace the fistula to its origin, usually to diseased bone. Operation is then always successful. In one case the injection was followed in a short time by healing of the fistula, although it had existed for two years and was due to tuberculous disease of the second and third lumbar vertebræ. The fistula has remained closed for two years. A similar result was obtained from a fistula in an old coxalgia, for which several radical oprations had been done

during a period of four years. This result was repeated in a third case, a tuberculous osteomyelitis of the knee. During two years' experience with this method many other cases were treated successfully. Of special interest was a case of empyema of the pleural cavity, which discharged four ounces of pus daily for nine months. It failed to improve under any treatment, and, finally, an Estlander operation was proposed. After ten injections given every other day, the fistula was completely healed and remained closed for three months, showing no signs of retention. Beck explains the results upon the principle of affording a scaffolding for the granulations and the subsequent cicatrix formation. He expects later to study the exact pathological findings and to report the results. Two bismuth mixtures are employed: one for diagnostic purposes and the other for later treatment. That for diagnosis consists of bismuth subnitrate 30 parts, and white vaseline 60 parts. That for the later treatment is made up of bismuth subnitrate 30 parts, white vaseline 60 parts, paraffin, soft, 5 parts, and wax 5 parts.

Two Cases of Traumatic Urinary Effusions in the Renal Region (Traumatic Pseudohydronephrosis).—NOVE-JOSSERAND and BALLIVET (*Arch. gén. d. chir.*, 1908, ii, 437) report two cases, in children resulting from a fall, of this relatively rare condition. In both an incision was made through the abdominal wall over the tumor, opening the peritoneum, through which the tumor was recognized as occupying the renal fossa. It was opened and evacuated and the margins of the opening in the tumor sutured to the edges of the parietal peritoneum of the abdominal incision, with drainage. The first patient recovered and the second died. An autopsy on the latter showed a stricture of the ureter about 15 cm. from its termination in the bladder. Of Monod's 27 cases, in 22 the age was noted and in these it occurred 13 times in children under fifteen years of age. It was the result of varied traumatisms. In almost all cases there was immediate pain more or less acute, accompanied by a mild grade of shock, without grave peritoneal disturbances or any of the classical signs of hemorrhage. In 2 of Monod's cases and 1 of the authors' the painful phenomena were completely absent. In 12 out of 27 cases the pain was accompanied by hematuria, always slight and coming on immediately or two or three days after the accident. The appearance of the tumor is never immediate, in the earliest case developing in ten days, ordinarily in only twenty to thirty days after the accident, sometimes after fifty to sixty days. It may progressively increase until it fills the loin space and passes over the median line anteriorly. It is largely filled with urine. The authors recognize two groups of cases: the first consisting of simple cases without preliminary lesions of the urinary apparatus, and the second of complex cases with persistent lesions of the kidney, ureter, or pelvis. When in the simple there is a small perirenal effusion without disturbing functional symptoms, one may wait, as a spontaneous cure may follow. If it persists one, two, or three successive punctures may be made. In case of incessant reproduction of the effusion, incision and marsupialization should be resorted to as in one of the authors' cases. Only exceptionally will nephrectomy be necessary. In the complex cases spontaneous cure has not been observed. A free opening should be made.

THERAPEUTICS.

UNDER THE CHARGE OF

REYNOLD WEBB WILCOX, M.D., LL.D.,

PROFESSOR OF MEDICINE AND THERAPEUTICS IN THE NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL; VISITING PHYSICIAN TO ST. MARK'S HOSPITAL,

ASSISTED BY

HENRY HUBBARD PELTON, A.M., M.D.,

ADJUNCT ASSISTANT ATTENDING PHYSICIAN TO THE BELLEVUE HOSPITAL; CHIEF OF THE MEDICAL CLINIC, PRESBYTERIAN HOSPITAL DISPENSARY, NEW YORK.

Serum in Scarlet Fever.—CUMPSTON (*British Medical Journal*, 1908, i, 1291) concludes his observations of the serum treatment of 42 scarlet fever patients with the statements that the recovery rate seemed better than usual, and that the earlier the serum was administered the better were the results. In many instances within forty-eight hours of the injection the temperature began to fall, the cervical glands began to subside, the necrosis of the throat began to clear, and the rhinorrhœa ceased or lost its purulent character. Not all patients did so well as this, but most did very much better than would have been expected under ordinary treatment. The author has the distinct impression that the injection of antiscarlatinal serum in doses of not less than about 12 drams, and as soon as the onset of nasal discharge, glandular swelling, fever, and signs of sepsis occur, will produce a marked improvement in septic instances of the disease. In the toxic type little can be said in favor of the use of the serum.

Psychotherapeutics.—DERCUM (*Therapeutic Gazette*, 1908, xxxii, 305) states that in applying psychotherapeutic methods we should always remember that the patient's symptoms have a physical basis: this is especially true in functional nervous diseases. States of exhaustion play a fundamental role in all of them, and when the general level of the mental tone is raised obsessions disappear. It would seem, then, that attention to the physical condition of the patient, the bringing of his health to the highest level, must be the first object of our treatment; in other words, simple physiological procedures, rest, full feeding, gentle exercise, bathing, massage and the like, should always be instituted. In obsessional states there is essentially a neurasthenia, or, to use the latter-day term, a psychasthenia; it is the underlying asthenia which first demands our attention. Rest and physiological measures can be applied in accordance with the character of the patient, from partial methods up to a full rest cure. Added to these conditions we should institute such simple psychotherapeutic measures as mental rest, especially such as is secured by the isolation of the patient; second, the restraining of the patient; later special mental exercises or mental gymnastics, if necessary. During all of the time judicious use should be made of normal suggestion, both direct and indirect. Under the latter we should include such an explanation to the patient

of his condition as may be adequate and tactful, pointing out that his symptoms are functional, and that they will in time disappear. That normal suggestion acts powerfully when the general health is improving goes without saying. Suggestion under hypnotism is rarely if ever justified. Psycho-analysis will probably, for reasons already given, never find a permanent place in our therapeutics.

The Alkalies in Bronchial Catarrh.—HAIG (*British Medical Journal*, 1908, i, 1100) has been accustomed to employ the salicylates in bronchial inflammations attributed to uric acid irritation or rheumatism. He finds that this form of treatment fails when the urinary acidity is low, and as the effect of dyspnœa, from which these patients often suffer, is to increase the alkalinity of the blood and lower the acidity of the urine, it follows that the salicylates will fail when dyspnœa is considerable and cardiac dilatation is beginning. Noting this, Haig began to try the alkalies in such patients, and found that it was only necessary to give the alkali in sufficient dosage to render the urine alkaline to bring about immediate relief in many instances. The alkali preferred is sodium bicarbonate in twenty-four hour dosage of 20 to 60 grains for a child and 90 to 120 grains for an adult. The alkali should not be combined with drugs which raise the urinary acidity or which act as a precipitant of uric acid, such as lime, the metals, or their salts, or even the chlorides, sulphates, or nitrates of the alkalies. Ammonium particularly should not be given, for it raises the urinary acidity and its urate is insoluble.

Rectal Injection of Antitoxic Sera.—PARKINSON (*Lancet*, 1908, i, 1273) advises the rectal administration of sera in those patients who object to the prick of the needle, and because when sera are given in this way there are never any untoward accidents such as may occur after hypodermic injections. He states that it is not certain that the rectal lining is absorbent of therapeutic sera, but asserts that their effects are quite as evident when given per rectum as when given in the more usual way. His technique is as follows: Cleansing enemas are not given unless their is marked constipation. The patient lies on the left side and a catheter is passed as far as possible into the rectum. To the catheter is attached a glass urethral syringe containing the serum. The fluid usually will flow in of itself, but if necessary the piston is used. After the injection the patient should remain in the recumbent for fifteen minutes. Instances of the administration of anti-streptococcic serum and of diphtheria antitoxin are cited.

Psychotherapy in Functional Neuroses.—HERRING (*New York Med. Jour.*, 1908, lxxxvii, 885) discusses this subject, in part, as follows: After a thorough physical and mental examination of a patient the physician assures himself that the affection is entirely functional; he can then institute rational psychotherapy and use as adjuncts the necessary physiological means to bring about a cure. Using either persuasion or suggestion, or both, because it will be a difficult matter to separate the two, he will state plainly the facts of the case to the patient, telling him what caused the trouble and explaining how the symptoms may be produced, the part the mind plays in originating and

fostering the various fears and distressing symptoms. The fact that these can be relieved and cured with his coöperation, and how this is to be brought about, are impressed upon him repeatedly. Patients of average intelligence will listen to this with interest, and the majority will enter into hearty coöperation with the doctor. The average patient will accept the statement of the physician, and will believe that he will get well, even after months of suffering. After once carefully listening to a recital of the symptoms and explaining each one, it is much better at subsequent visits not to refer to them again or allow the patient to refer to them. Keep the one idea always in view that the symptoms will disappear and that entire recovery will take place. When the patient requires treatment other than that which is purely psychic, one should not hesitate to use dietetics, electrotherapy, hydrotherapy, pharmacotherapy, or any physiological means to bring about recovery. Psychotherapy should not tend to make us therapeutic nihilists.

Serum Treatment of Exophthalmic Goitre.—BLUMENTHAL (*Folia Therapeutica*, 1908, ii, 62) has used both an antithyroid serum, which represents the blood serum of thyroidectomized sheep, and an alcohol-ether precipitate of the milk of thyroidectomized goats in the treatment of this disease, and finds that the former is decidedly more potent than the latter. The dose of the serum is, at first, 10 drops thrice daily, increased to double this amount, gradually dropped to 5 drops, three times a day as improvement takes place. Sometimes the serum causes palpitation, in which case the less active powdered precipitate is substituted; its beginning dosage is 75 grains per day increased gradually to six times this quantity. The dosage must be varied in accordance with the patient's response to the treatment. The serum is usually well borne and its administration usually results in a softening and sometimes in a diminution in size of the thyroid gland; the œsophageal and tracheal pressure for the most part ceases, and the exophthalmos becomes less marked, although the tachycardia often remains uninfluenced. The treatment always influences the subjective symptoms, the insomnia yields, in most instances, within a few days, the perspiration diminishes, the palpitation and feeling of distress improve and the body weight is increased. It is of course necessary to continue the treatment for months or years. The great disadvantage is that the improvement may be so slow that the patient becomes discontented and unwilling to persist in it. The author considers that this treatment is preferable to operation on account of the danger of the latter and since the end-results of surgical interference are not completely favorable.

Organotherapy in Exophthalmic Goitre.—RENON and DELILLE (*Tribune Méd.*, 1908, xli, 281) have employed the extract of the hypophysis in this disease on account of the known effect of this substance upon arterial tension, tachycardia, and the thyroid gland. A number of their patients have been benefited, but no cures were effected. It appears logical to treat exophthalmic goitre with the glycerinized blood of animals deprived of the thyroid gland combined with pituitary extract, since hemato-ethyroidine neutralizes the effect of thyroid hypersecretion and since the pituitary body exercises a general vasoconstrictor effect. The two treatments may be associated by giving the patient each day

2 to 3 teaspoonsful of hemato-ethyroidine and 3 to 6 grains of powdered pituitary extract. After twenty days of treatment an interval of eight days is advised; other series of treatment are prescribed in accordiance with the effect produced. Another method is to administer the hemato-ethyroidine alone for fifteen days, after which the pituitary extract is given for a similar period. This combined organotherapy based on physiological, pathological, and general therapeutic principles gives better results than either form of treatment alone, and causes remarkable remissions in the symptoms of exophthalmic goitre.

The X-rays in Leukemia.—TAUSSIG (*Interstate Med. Jour.*, 1908, xv, 439) reports three instances of leukemia treated by the Röntgen-rays and sums up our knowledge of this form of treatment as follows: Reports of apparent cures of leukemia by means of the *x*-rays were received with great enthusiasm, and it was believed that a cure for this disease had been discovered, but, unfortunately, these sanguine expectations have not proved well founded. One after another, the patients, thought to have been cured, relapsed and died, so that it seems established that in the *x*-ray treatment of leukemia we have a palliative, never a really curative, agent. Nevertheless it is our most potent therapeutic method in this disease. It would seem that in myelogenous leukemia the rays exert a favorable influence in about 90 per cent. of patients. The patients becomes subjectively well and only the demonstration of a slight splenic tumor and of an occasional myelocyte in the blood serve to remind us that the disease is only latent. Sooner or later the inevitable relapse occurs and then the rays usually prove far less effective than at first; the total duration of the disease is still usually less than one year, rarely more than two, but meanwhile the patient has had months of apparent health. In lymphatic leukemia the rays have proved far less effective than in the myelogenous type. Here the blood is but slightly affected and only those lymph nodes which have been directly exposed to the rays show any tendency to atrophy. Occasionally, however, results have been obtained rivalling those in myelogenous leukemia. At all events, even in lymphatic leukemia, the *x*-ray treatment deserves a trial.

Marmorek's Serum in Tuberculosis.—UHRY (*Revue Francaise de Méd. et de Chir.*, 1908, vi, 135) has treated 48 patients with Marmorek's serum; of these 11 were affected with surgical tuberculosis and 37 were the subjects of pulmonary tuberculosis in different stages. Of the 11 instances of surgical tuberculosis, 10 were cured and 1 was greatly benefited. Of the 15 instances of pulmonary tuberculosis of the first degree 13 were cured; notable amelioration took place in 2 who have been so lately treated that further prognosis in uncertain. Of 21 patients in the second and third stages 3 were entirely cured, 10 much improved, and 8 have died. No untoward effects of any consequence were observed during the treatment even when daily doses as large as 6½ drams were employed. Slight pain at the site of the injections sometimes was noticed and twice a slight urticaria was remarked. The treatment seems to be absolutely harmless.

PEDIATRICS

UNDER THE CHARGE OF
LOUIS STARR, M.D., AND THOMPSON S. WESTCOTT, M.D.,
OF PHILADELPHIA.

Whooping-cough, Complicated by Acute Nephritis, Lobular Pneumonia, and Left-sided Hemiplegia.—This remarkable case, which terminated in recovery, is reported by A. E. BLACKBURN (*Jour. Amer. Med. Assoc.*, 1908, i, 530). A child, aged four and one-half years, had been suffering with whooping-cough for six weeks, during which time he was not under the care of a physician. He spent a great deal of time in the open air during a period of extreme dampness and cold. He was seized suddenly with a general convulsion, followed immediately by coma. Other causes having been eliminated, the child was catheterized and albumin in large quantities found in the urine. During the uremic state the temperature rose to 108°, the child was pulseless, and respirations were very high. The coma lasted for ten days. A few days later the right upper lobe showed signs of consolidation anteriorly, and during this the temperature again rose to 107°, the pulse again became impalpable and death seemed imminent. Inability to expectorate several times almost caused death through strangulation, but the crisis was safely passed, when constant convulsive movements were noticed in the right side; the right arm and leg could be moved, but not the left. A complete left-sided paralysis, involving the left arm, leg, side of the face, and the left external rectus was noted as the child became sufficiently conscious. The nephritis gradually disappeared, the pneumonia resolved, and the cough again became whooping in character; it finally disappeared. Seven months after the onset the patient walked with a halt and the left arm was weaker than the right; otherwise he had completely recovered. The stimulation throughout was rather vigorous for a child so young.

A New Constituent of Milk (Lactoconium).—A. KREIDL and A. NEUMANN (*Wien. klin. Woch.*, 1908, xxi, 214) report examining the milk of different species (cow, rabbit, guinea-pig, dog, cat, and woman) with the ultramicroscope. They discovered in the milk of the lower animals a corpuscular constituent, which they could not find in the milk of woman. The milk of the animals contained a large number of small particles, which were in constant violent molecular movement. These the authors propose to call lactoconia, until their true nature is discovered.

Parathyroidal Meningitis in Infants.—Two such cases are reported by L. ARTZ and J. BOESE (*Wien. klin. Woch.*, 1908, xxi, 217) in infants respectively seven weeks and five months old. In both cases the primary conditions had been gastro-enteritis, in the course of which the meningitis developed. In both instances Gram-positive cocci were isolated, which, in the second case, at least, could positively be identified with the paratyphoid bacillus of Schottmüller. It was agglutinated

by the immune serum from the Bacterium paratyphus Schottmüller B., and the serum from it agglutinated the corresponding emulsions of bacteria. The agglutination was noted in as high a dilution as 1 to 24,000, the exposure being one-half hour at room temperature. In the case of the coccus from the first case agglutination occurred only in dilutions of 1 to 1000, but in spite of this a similar conclusion could be arrived at. This shows that paratyphoid infections occur at a very early age, probably by way of the intestinal tract and lead to a bacteremia. As there are many cases of fibropurulent meningitis in childhood, the authors suggest, in view of the already large number of cases of typhoid and colon meningitis described in children, that all bacteriological and serodiagnostic aids should be employed to discover the exact nature of every case of meningitis in infants and children.

The Influence of Thyroidal Feeding upon the Nitrogenous Metabolism of Children.—A. Orgler (*Zeit. f. exper. Path.*, 1908, v, 1) performed his experiments to determine the influence of large amounts of thyroid substance upon the general health, the pulse, and respirations of infants and children. The usual reports are that they react entirely differently from adults; another object of his observations was, whether they do not react at all or simply compensate the injuries better. The amount of nitrogen and uric acid was determined; four children were given large quantities of fresh thyroidal substance, two others were given potassium iodide, and one iodeigon; the latter to determine the influence of an organic iodide, and artificially iodized albumin. In addition to the thyroid gland, the children were given only milk and zwieback. The general health of all remained perfectly good is spite of the large amount of thyroid gland given; the pulse and respiration were not influenced in the slightest. In every case a larger amount of nitrogen was excreted, however, than was taken in. In the case of the three children given iodides and iodeigon, the nitrogen excretion was not increased. The body weight in two of the children fed with thyroid decreased; in the others it remained stationary.

The Value of the Suprarenal Glands in the Pathology and Treatment of Rachitis.—Stoelzner, after feeding a number of children at the Berlin pediatric clinic with suprarenal substance, reported marked improvement in rachitic symptoms due to retention of calcium salts. The symptoms which, in particular, improved were the sweats, craniotabes, slow dentition, sensitiveness to pain, restlessness, and vasomotor irritability; the children learned to sit, stand, and walk at a much earlier period than other rachitics. The abnormality of the thorax and verterbal column diminished, the fontanelle became smaller, the rachitic rosary and the epiphyseal swellings of the long bones disappeared. Stoelzner believed this improvement to be due to the retention of lime salts after feeding with suprarenal substance. To note the truth or falsity of this theory R. Ouest (*Zeit. f. exper. Path.*, 1908, v, 43) performed a number of experiments with young dogs, determining the excretion of the calcium and the nitrogen. He could not determine a retention, but could observe an unfavorable influence upon the calcium metabolism, which lasted not only while the dogs were being fed, but also for some time after. A number of clinical observations have also refuted the theory of Stoelzner, and it therefore seems probable that suprarenal

extract has no more influence on rickets than have other organic substances as thyroidin, thymus extract, etc. The glycosuria and arteriosclerosis noted in these and other reported experiments are due not only to increase in blood pressure, but much more so to a toxic action of the adrenalin upon the entire organism.

Rennet Coagulation in the Stomach of Nursing Infants.—The question whether the cheese clots forming in the stomachs of nursing animals and infants are formed by rennin or hydrochloric acid has been studied and solved by A. KREIDL and A. NEUMANN (*Zentralbl. f. Physiol.*, 1908, xxii, 133) by means of the ultramicroscope. Casein clots produced by the action of acids could be seen by the ultramicroscope to return to their original fine emulsion before dissolving, when sodium hydrate was added; the clots produced through coagulation with rennin were dissolved by the alkali without returning to this stage. Milk clots from the stomach of nursing animals, as well as clots from the stomach of an infant fed with cow's milk, were dissolved directly by the rennin, thus showing that in all probability the milk in the nursing infant's stomach is clotted by the rennin and not the hydrochloric acid. That the same is true of human milk is more than probable, as the infant's stomach contains active rennin, and is acid in reaction, and it has been shown in vitro that human milk is coagulated by rennin.

An Analysis of 500 Cases of Spinal Infantile Paralysis.—J. COLLINS and T. H. ROMEISER (*Jour. Amer. Med. Assoc.*, 1908, i, 1766) present, in tabulated form, the analysis of 500 cases of spinal infantile paralysis, 327 of which they observed during the epidemic of 1907 and 173 previous to it. There were 297 males and 203 females; 311 developed in the months of July, August, and September; 62 were less than one year old, 158 between one and two years, and 134 between two and three years, thus showing that by far the greater number are less than three years old. High fever was noted in 145, slight fever in 191, no fever in 29; in 261 patients it lasted less than four days; in 100 more than four days. Vomiting was recorded in 151, anorexia in 78, diarrhœa in 49, constipation in 88, retention in 37, incontinence in 5, somnolence in 87, stupor in 40, unconsciousness in 10, rigidity and retraction in 56, insomnia and restless in 34, twitching in 66, convulsions in 18, delirium in 18, screaming in 32, crying in 59, and immotility in 59. One leg was paralyzed in 216, both legs in 134; in 65 the lumbar and gluteal muscles; in 36 one arm and in 5 both; in 35 cranial nerves were affected; 32 had quadriplegia, 27 triplegia, in 29 the abdomen and diaphragm and in the same number the neck muscles, in 20 the back muscles, in 15 the rectus occuli, in 14 the larynx and tongue, in 9 the facial muscles and also those of the chest, in 6 the sphincters, and in 3 the pharynx. The lumbar enlargement is oftenest affected, next the cervical and then the dorsal, not infrequently also the bulbar structures. The diaphragm was paralyzed only once. Trauma was noted very rarely as a preceding factor; most of the children previously were in the best of health; the paralysis was usually noted two to four days after the onset of the disease. Both ascending and descending Landry types of paralysis were observed. The infection finds the entire central nervous system and its coverings susceptible. A considerable number of their patients made a fair recovery.

OBSTETRICS.

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Prolapse of the Normally Situated Placenta.—STERN (*Monats. f. Geb. u. Gynäk.*, 1908, xxvii) reports the interesting case of a patient in her ninth pregnancy. Previous pregnancies had all been terminated by artificial help. There was no history as to the course of the third stage of labor in these cases. The present pregnancy had proceeded without disturbance. There was no sign of hemorrhage whatever. Stern was summoned to the patient by a midwife, because spontaneous labor had ceased. On examination the abdomen was greatly distended. The amniotic liquid was excessive in amount. The fœtus was small. The heart sounds were very faintly heard, and the fœtus occupied a transverse position. Uterine contractions were strong and there was no hemorrhage. On internal examination the cervix was completely dilated, the membranes unruptured and tense, and no evidence could be found of the placenta. An effort was made to turn the child internally, but this failed. The membranes were ruptured between the pains and the hand introduced to perform version. As soon as the membranes were ruptured a very strong pain developed, which closed the cervix so that but two fingers could be inserted. The amniotic liquid escaped freely, although the hand and arm were used as a plug to prevent its entire loss. As the last of the fluid escaped it was noticed that it was blood tinged. The uterus relaxed after the membranes were ruptured, and the finger on entering the cervix found the placenta. As the hand was introduced the entire placenta was found lying detached at the internal os. The child was immediately turned and extracted, and although it breathed a few times it did not survive. The placenta issued from the uterus without uterine contractions as soon as the head of the child escaped. The placenta was entire and there was no large retroplacental blood clot. The membranes had ruptured about 10 cm. from the border of the placenta, which was one of the points against placenta prævia. Examination of the body of the child showed death from asphyxia. These cases are to be distinguished from placenta prævia in its various forms, accidental separation of the normally implanted placenta accompanied by hemorrhage. In the present instance there was no hemorrhage either before, after, or during labor, and the placenta could not be found on internal examination until the cervix was completely dilated and the child was about to emerge. In the case cited the occurrence of polyhydramnios had undoubtedly something to do with the prolapse of the placenta. The sudden and great change in the intra-uterine tension following the escape of the amniotic liquid, may have been largely instrumental in the prolapse. As a predisposing cause of this accident one must recognize the abnormal conditions in the endometrium and the decidua, which are so frequently seen in placenta prævia.

Chorio-epithelioma, with Metastasis in the Vagina.—BRENNER (*Monats. f. Geburts. u. Gynäk.*, 1908, xxvii) concludes an interesting paper upon this subject. The case which he describes had never belonged in the category of cases of beginning typical malignant chorio-epithelioma, and arose from the proliferation of villi following the development of vesicular mole. The growth of the syncytium and its proliferated cells occurred in Langhans' layer; the wandering cells of the chorion arose from both Langhans' layer and the synctium. This could be demonstrated in the case reported. The development of the placenta seemed to be normal, but elements partly placental and partly foreign seemed to develop in the chorio-epithelioma. The character of the growth was essentially malignant, and its predominating feature was the rapid dissemination of syncytium. The degree of malignancy seems to depend upon the development of tissue in the tumor and tissue in the maternal organism as well. It is practically impossible to differentiate between the two. It is not yet clearly established that the syncytium arises from the chorion only; it may develop in part from the maternal tissue; in both epithelial and endothelial tissues are concerned. In the matter of diagnosis and prognosis the histological study of a given tumor is most important. When the tissues about the tumor are involved, operation should be preferably done by the vaginal route.

Extirpation of the Uterus for Difficult Labor following Vaginal Fixation.—ROSTHORN (*Monats. f. Geburts. u. Gynäk.*, 1908, xxvii) reports the case of a multipara who, two years previous to coming to the hospital, had vaginal fixation of the uterus done. During pregnancy there was great distention in the pelvic veins and those of the lower extremities. There was also disturbance in the function of the bladder. Labor developed very feebly and abnormally; the fœtus was in transverse position; the uterus enormously enlarged transversely, and there was no possibility for spontaneous labor. In endeavoring to introduce an elastic bag to dilate the cervix, the posterior vaginal wall, which was greatly stretched was ruptured; this was followed by very free hemorrhage which was controlled with difficulty by tampons. The abdomen was at once opened, the uterus opened, the child extracted, and the placenta removed. The posterior wall of the uterus was enormously distended and very thin; the anterior intra-uterine wall, over an area as large as the hand, was closely adherent to the vagina. A gauze tampon was used to shut off the abdominal cavity from the pelvis. The patient made a good recovery complicated by phlebitis in the lower extremity. On examining the uterus its contour had been completely altered and spontaneous labor, or even delivery by any method except section, would have been impossible.

The Supports in Chief of the Female Pelvic Viscera.—PARAMORE (*Jour. Obstet. and Gynec. Brit. Emp.*, June, 1908) reviews the literature of this subject and discusses the part played by intra-abdominal pressure and the levator ani muscle. He concludes that the pelvic viscera are maintained in their position by two sets of forces: The one acting from above pins the viscera in their position; this is the intra-abdominal pressure. The other from below supports the viscera and prevents them from being displaced by excessive force from above. These two forces

vary with each other; the increase of the one produces the increase of the other. Both of these factors are under the control of the nervous system. The most essential element in maintaining the normal visceral position is supplied by the levator ani muscle. During defecation the visceral connective tissue is capable of supporting the viscera temporarily, but it is not capable of more than this. When this muscle becomes insufficient the viscera prolapse after a time.

In the same Journal, Fothergill discusses the pathology and operative treatment of displacement of the pelvic viscera. He concludes that in cases of classical prolapse anterior colporrhaphy, with union in the middle line of the parametric and paravaginal tissues, is indicated; with this should be performed posterior colporrhaphy and closure of the perineum. Ventrofixation in patients in whom conception cannot occur is indicated in addition, if necessary. When cystocele and vaginal prolapse are present, anterior colporrhaphy and closure of the perineum and pelvic floor are indicated. When the uterus is persistently retroverted and movable Alexander's operation is indicated, and when the uterus is fixed, abdominal section should be performed, adhesions separated, diseased appendages removed, and the uterus secured in anteversion.

The Excretion of Creatinin in Puerperal Patients and its Relation to Involution of the Uterus.—LONGRIDGE (*Jour. Obstet. and Gynec. Brit. Emp.*, June, 1908) made observations upon ten patients delivered in Queen Charlotte's Hospital, who had normal labors and recoveries. The patient's diet was regulated, consisting of milk, eggs, porridge, and bread and butter. The total nitrogen of the urine was estimated and the creatinin was determined by Folin's method. The percentage of nitrogen excreted as creatinin during the nine days following delivery varied from 4.2 on the first day to 3.2 on the ninth day. The average percentage for the whole puerperal period for creatinin is practically 3, which is the normal one for the excretion of endogenous creatinin. If creatinin is manufactured by muscular autolysis then its percentage should have been increased in these patients under the muscular exertion of labor. These results indicate that autolysis of the uterine muscle does not occur in normal cases. These results are in accord with those of Mellanby, who found in experiments in which bacteria were eliminated that creatin and creatinin are not produced by muscular contraction. The excretion of total nitrogen in these cases showed increase on the fifth and sixth days, and then decrease. During the first four days it varied but little. It seems rational to believe that this is the result of uterine involution. The uterus loses half its weight in normal involution during the first week, probably due to the comparative anemia of the uterus. This, however, is not entirely the result of anemia. Longridge believes that the development of sarcolactic acid in the uterine wall after delivery favors autolysis. After labor the uterus is left, if well contracted, in a comparatively anemic condition with diminished alkalinity. These two factors favor rapid autolysis. As the uterus becomes softer and the blood passes freely through it, it becomes alkaline, the products of autolysis are gradually removed, and its rate very much diminished. In rare cases, in which the patient loses blood greatly after labor, the uterus may undergo excessive involution and practically disappear.

GYNECOLOGY

UNDER THE CHARGE OF

J. WESLEY BOVÉE, M.D.,

PROFESSOR OF GYNECOLOGY IN THE GEORGE WASHINGTON UNIVERSITY, WASHINGTON, D. C.

Early Tubal Gestation: A Clinical Study.—A. C. HERMAN SUHR (*Jour. Obst. and Gyn., Brit. Empire,* 1908, xiii, 261) has carefully studied a series of 109 cases of early tubal gestation with special reference to operative and palliative treatment. Suhr states the present ideas on treatment are somewhat as follows: (1) There is a consensus of opinion with regard to the very serious cases, which show obvious signs of severe internal hemorrhage, that there is only one course open, namely, immediate laparotomy. Dispute is confined almost entirely to the various types of less serious cases, such as the following: (2) In women presenting sufficiently obvious signs of a serious condition, such as the formation of a pelvic hematocele, and having, as a rule, had several attacks of severe abdominal pain, the general opinion is now in favor of operation without unnecessary delay, and Suhr says the experience of this series will show that this opinion is justified. (3) There is another type of case in which the treatment is perhaps most in dispute. These are cases in which the signs and symptoms are slight or have occurred some time before the patient comes under observation. It is probable that the ovum has perished and that the risk is over. It is from these cases that the largest number is chosen for expectant treatment, a course which Suhr endeavors to show to be by no means free from danger. (4) There are cases in which the ovum has been retained for some considerable time. Even in such cases there is evidence that there is danger in leaving them to nature.

To the 88 cases taken from the St. Thomas Hospital Reports by H. Bell, Suhr has added 21 he has minutely studied. Of the 21 but 17 cases were operated upon. No mortality ensued. Of the 109 cases 13 were left alone and recovered and 3 died after operation. Vaginal section was done 6 times, and is not recommended; 90 cases were subjected to abdominal section (80 primarily and 10 secondarily) with 3 deaths.

In several the fœtus was found living at operation a number of weeks after the first symptoms of rupture. In one case the patient was kept under observation three months when urgent operation was required. The deaths were in two instances the result of curettage and infection of the hematocele under a wrong diagnosis before section was made, and in the other from operation for uncontrollable hemorrhage in a case under observation in the hospital. Suhr believes that there can be no question that cases with signs of severe internal hemorrhage require immediate operation and that we are not at present qualified to select our cases, and until we are able to do so with certainty it is best to operate. He lays particular stress on the point that in but one case in which only abdominal section was the treatment did death occur. It

might be added that in that instance the delay of the operation incident to palliative treatment is probably responsible for the fatal ending. He states a change in methods shown by the newer series (21 cases) is the complete demise of vaginal section as a method of operative procedure. As a primary operative method it has shown itself to be dangerous and useless, and has recently been employed only as a method of drainage. Suhr's paper is ended by these conclusions: (1) The tendency toward more frequent operation is justified and the results are much improved; (2) the risk of abdominal section is not greater than the risk of leaving cases without operation, and (3) we are at present unqualified to select with safety cases for expectant treatment.

Two Cases of Multilocular Retroperitoneal Cysts in Women.—ALBERT DORAN (*Jour. Obstet. and Gyn., Brit. Empire.*, 1908, xii, 257) mentions 2 cases, one in a girl aged fifteen years, and the other in a woman aged thirty-nine years. Both were situated on the left side and extended from the pelvis to the ribs. In one the descending colon was on the outer side, and in the other in front of the tumor. Large bloodvessels passed from the mesenteries to the capsule in each instance. The kidney was behind the tumor in each case and the adrenal had no apparent relation to the tumors. Neither had a pedicle. The cyst walls were very thin and the contained fluid was clear and thin. The cyst wall was found to be made up of almost pure fibrous tissue without any adrenal, glandular, sarcomatous, or carcinomatous elements. They are believed to have developed from the Wolffian bodies. One has had no recurrence in the subsequent twenty-two years and the other for a number of years.

The Occurrence of Ovarian Tumors in Sisters.—A. C. BUTLER-SMYTHE (*Jour. Obst. and Gyn., Brit. Empire*, 1908, xiii, 266) records three instances of this character in which he operated on the six patients. In each instance one sister was single and the other married. In the first the unmarried sister had two large multilocular cysts; the other a large multilocular cyst and a large cystic ovary. In the second each sister had a dermoid tumor of the left ovary. In the third each sister had a multilocular tumor of the right ovary and both patients were said to be pregnant. In all three instances the sisters from each family were operated on consecutively. All of the patients came under notice within the period of sexual life.

Fistula between the Fundus of the Uterus and the Upper Portion of the Intestine.—WILLIAM F. GRAVES (*Amer. Jour.* Obst., 1908, lvii, 353) reports a case of this kind that occurred in a woman, aged thirty-eight years. Graves had first seen the patient six weeks after she had been delivered instrumentally of a dead child, at which time the uterus was supposed to have been ruptured, a loop of intestines removed through the uterus, and a constant fecal discharge through the vagina resulting. Abdominal section made May 24, 1907, revealed a mass of intestine matted together in the left side of the pelvis by adhesions which were thoroughly freed with little damage to the bowel wall. The intestine,

less than two feet from the duodenum, had been severed completely. The upper end of the jejunum passed directly into the upper portion of the left broad ligament and was attached clearly to the uterus just below the left horn. It was adherent to the uterus and the cavities of these two organs connected through an aperture 2 c.c. in diameter. The lower segment was completely sealed above by adhesions to the wall of the false pelvis several inches away from the end of the upper segment. Intestinal anastomosis with closure of the fistula was successful.

High Rectocele after Perineal Repair.—R. L. DICKINSON (*Amer. Jour. Obst.*, 1908, lvii, 347) in discussing this subject says the factors in the production of rectocle seem to be: (1) Laceration or lack of tone in the fascia and muscles of the pelvic floor. (2) Injury to the muscular layers of the rectal wall, or defective activity of such layers. (3) Defects in conformation of the rectum, or in the axis of the rectal canal, or of the anal canal or both. (4) Obstruction from vigor or irritability of the sphincter. Dickinson comments on the unreliability of post-mortem observations on the configuration and tonicity of the rectal and anal canal and on the falsification due to the relaxation from anesthesia. His methods of study upon the conscious subject are: (1) The rectum is distended with air and viewed with specula, either in the knee-chest posture or the lithotomy position with the head lowered; (2) by digital touch; and (3) by tracing tape or wire, the resultant measurements and angles being plotted on a full-sized sketch. Special points are noted by specular and digital examinations, and by means of the lead tape or solder wire running from the pubic crest to the sacrum with little slides on it which are placed at the coccyx, anus, fourchette, and crest of the rectocele, a tracing is made which together with the rectal examinations afford data for a definite appreciation of the injury to the rectovaginal partition. To prevent high rectocele, after repair of perineal injuries, it is necessary to make a digital rectal examination of the septum without general anesthesia; to identify the structures properly at operation, and to institute a very systematic after-care of the patient. This last precaution Dickinson considers highly important.

Voluminous Multilocular Ovarian Cyst in a Woman Aged Seventy-three Years.—A DELETREZ (*Ann. de gyn. et d'obst.*, 1908, v, 231) has recorded a case of this disease in which he removed the tumor, weighing eighty-eight pounds, the contents of which were colloid in character. The tumor had ruptured spontaneously before operation. The patient recovered sufficiently to leave the hospital eighteen days after the operation.

OPHTHALMOLOGY.

UNDER THE CHARGE OF

EDWARD JACKSON, A.M., M.D.,

OF DENVER, COLORADO,

AND

T. B. SCHNEIDEMAN, A.M., M.D.,

PROFESSOR OF DISEASES OF THE EYE IN THE PHILADELPHIA POLYCLINIC.

Oculopalpebral Epithelioma; Accidental Cure of Blindness.—DUJARDIN (*Clin. Ophtal.* No. 8, 1908, p. 119) reports a remarkable case in which a large epithelioma beginning at the margin of the lower lid and extending across the entire cornea completely concealing it with, of course, total blindness of the eye. Immediately upon striking his head accidentally against a tree the affected eye received a violent contusion with profuse hemorrhage. When this was arrested the man found that he had recovered his sight. The cornea was found entirely uncovered and intact and the remains of the tumor formed a thick fringe about the lower border on the nasal side. Instead of forming an integral part of the cornea the tumor was evidently simply superimposed upon that membrane which retained its transparency intact. A few similar cases have been previously reported. It may therefore be advisable, in tumor of the anterior segment of the eyeball, to make a careful dissection to determine the condition of the subjacent cornea.

When Glasses are not to be Prescribed.—JACKSON (*Amer. Jour. Ophthal.* January, 1908, i) urges that glasses are not to be prescribed under the following conditions: (1) When there is no ametropia or eyestrain. (2) When ametropia is present, but does not limit the power of vision, or cause discomfort, or harm of any kind. (3) If the symptoms present, although such as are likely to rise from ametropia are probably due to other causes. (4) In the case of eyestrain connected with imbalance of the ocular muscles, it is too frequently expected that spectacles will give relief. Sometimes they do; sometimes they are a necessary adjuvant to other treatment. But in a large proportion of cases the fault lies in the central nervous system, the general nutrition of the patient, or his habits of life. (5) Spectacles should not be prescribed without an accurate knowledge of the error of refraction to be corrected. Of the ten thousand combinations that might be made from the trial case 9990 would not give any relief. The system will take drugs poured into it and dispose of them in some way usually without serious ill effects in a short time; but the effects of glasses for good or ill continue so long as they are worn. (6) Colored glasses are only indicated for some temporary purpose and not for permanent hypersensitiveness as to light. The latter is an indication for rest of the eye.

Defect of Abduction Associated with Retraction of the Globe in Adduction.—GREEN'S (*Ophthalmic Record*, February, 1908, 62) case presented all the features typical of the syndrome as laid down by Duane: that is,

partial absence of outward movement, partial deficiency of inward movement, retraction of the globe in adduction, a sharply oblique movement up and in and down and in, in adduction, paresis of convergence, and narrowing of the palpebral fissure. The absence of adduction probably indicates that the externus is replaced by an inextensible cord. The restriction of adduction may be due to inability of the normally inserted internus from exerting its full function with an inelastic externus or the internus may be inserted too far back on the globe, its function being inefficiently assumed by the superior and inferior recti. The recession of the eyeball into the orbit is explained by some to be due to the hugging of the globe between the inelastic externus and the contracting internus; by others to the oblique line of pull of the superior and inferior recti. The oblique movements observed in adduction are believed by Duane to be due to spasmodic action of the inferior or superior oblique, probably often combined with spasm of the superior or inferior rectus. Much uncertainty exists as to the cause of the narrowing of the palpebral fissure; Harman ascribes this simply to falling in of the lids from loss of their natural support when the globe is retracted. The insufficiency of convergence appears to be due to mechanical hampering of the internus. Tenotomy is hardly justifiable, while advancement is contra-indicated. Duane was able to collect 54 instances of this condition, of which 6 were observed by himself, whence it is probable that it is less rare than appears, being at times overlooked or incorrectly interpreted.

Osteoma of the Orbit.—Birch-Hirschfeld (*Clin. Ophtal.*, No. 19, 1907, p. 286) reports three operations for osteoma of the orbit, of which one resulted in death. Unoperated osteoma is far from benign as some believe. The risk if unoperated is greater than when the tumor is removed. The operative dangers can be lessened by early diagnosis, rapidity of technique (injury of the base is especially to be avoided), and by treatment of the inflammatory affections of the frontal sinus which frequently accompany the growth. Microscopic preparations from these cases showed that ossification is, as in the normal bone, endochondral and perichondral and periosteal, and not solely periosteal as has been stated.

Family Nystagmus.—In Apert's and Dubosc's cases (*Ophthalmoscope*, September, 1907, 399) a family of 10 children, 4 by the first husband and 6 by a second, all of the latter were affected with nystagmus without evidence of ocular or general disease, except that in three of the children the knee jerks were exaggerated. The father was dyspeptic, had always been subject to violent migraine, neuralgia, and pain. His mother had suffered from temporary auditory hallucinations. Of the 4 chidren by the first marriage, 3 unaffected children were dead, while one, aged thirteen years, had no nystagmus, but was affected with fibrillary twitchings of the muscles of the lips, especially the upper, coming on every two or three minutes. The reporters think that their cases were instances of myoclonic nystagmus of the hereditofamilial variety described by Lenoble and Aubineau.

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF
WARFIELD T. LONGCOPE, M.D.,
DIRECTOR OF THE AYER CLINICAL LABORATORY, PENNSYLVANIA HOSPITAL,
ASSISTED BY
G. CANBY ROBINSON, M.D.,
RESIDENT PHYSICIAN, PENNSYLVANIA HOSPITAL, PHILADELPHIA.

The Coronary Arteries of the Human Heart.—MERKEL (*Verhandl. der deut. path. Gesell.*, 1907, 10*th Tagung.*, 127) in trying to explain the lack of lesions in the myocardium in a case in which the left coronary artery was occluded has devised a very ingenious method of studying the distribution of the coronary arteries. The vessels are injected with red lead, mixed preferably with gelatin. The heart is hardened in formalin, and later is skiagraphed by a method which permits of the examination of the picture with a Bartholdy stereoscope. Of particular interest was the blood supply of the septum. To the anterior portion of the ventricular septum the left coronary furnishes large and numerous branches, while to the posterior half go smaller twigs from the circumflex branch of the right coronary. Under normal conditions communicating branches were found in the septum between these vessels. Anastomoses were likewise observed in the auricular septum. In hypertrophy of the heart an astonishing increase in the vascularity of the heart was found; the right coronary artery entered into this in a slight degree, but it was principally noticeable in the branches of the left artery. In certain cases extremely large vessels anastomosed in the ventricular septum, even when there were no anastomoses on the surface of the heart. The author believes this is significant in explaining the occurrence and the absence of myocardial lesions following disease of the coronary arteries.

The Relationship of the Neighboring Vessels to Angiomas of the Skin.—A. OPPENHEIM (*Frankfurter Zeit. f. Path.*, 1907, i, 124) injected into a freshly excised nevus a solution of Berlin blue. The piece of tissue was first dipped into paraffin to prevent the escape of the solution from the open ends of the vessels of the subcutaneous tissue. Thick sections were then cut and studied with the microstereoscope. By this means it could be determined that the normal bloodvessels of the surrounding subcutaneous tissue connected directly with angioma. At the base of the angioma the bloodvessels, which formed the tumor, were of their usual size, but toward the surface they branched out like the cords of a whip, became unusually wide, and formed coils.

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All communications should be addressed to—

DR. A. O. J. KELLY, 1911 Pine Street, Philadelphia, U. S. A.

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